EXHIBIT A

SMITH KLINE & FRENCH LABORATORIES LIMITED and SMITHKLINE BEECHAM CORPORATION d/b/a GLAXOSMITHKLINE, Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	)	Civil Action No. 05-197-GMS

EXPERT REPORT OF EGON E. BERG

1. I am an attorney specializing in the area of patent and trademark law. I am a member of the New York and District of Columbia Bars and have been admitted to practice before the United States Patent & Trademark Office ("Patent Office") for over forty years.

2. I have been retained by Wilmer Cutler Pickering Hale and Dorr LLP, on behalf of the Plaintiff GlaxoSmithKline ("GSK"), to provide my opinions regarding the Defendant Teva Pharmaceutical USA, Inc.'s ("Teva") allegations of inequitable conduct in this case.

3. I am being compensated for my time spent in connection with rendering my opinions in this case at my customary rate of $350 per hour. My compensation is not contingent in any way upon the conclusions or opinions I reach, any testimony I may give, or the outcome of this case.

4. My curriculum vitae describing my educational background and work experience is attached as Attachment A to this report.

5. In the last four years, I have not been deposed, nor have I testified at trial as an expert.

6. This report summarizes my opinions regarding the topics for which I have been asked by GSK to offer expert testimony, as well as the basis for my opinions. I reserve the right to revise this report as additional information becomes available.

7. For a list of documents and sources that I have considered in formulating my opinion in this case, please see Attachment B.

SUMMARY

8. I have been asked to offer my opinions regarding two inequitable conduct issues in this case in light of the standard practices of lawyers who draft patent applications and the patent examiners who review them. Because of my varied background as a patent examiner at the United States Patent & Trademark Office (with a focus in organic chemistry), a private practitioner, and an attorney with thirty-three years of experience at a pharmaceutical corporation, I believe I can bring unique perspective to the standard practices in the field in which I have actively participated for nearly forty-seven years. I continue to be active in the field as I currently consult for large and small pharmaceutical companies.

9. Based upon this experience and upon certain factual assumptions that have been provided to me, it is my opinion that there is no basis for a finding of inequitable conduct with respect to the scope of the generic claims presented by the applicant to the patent examiner in the United States Patent & Trademark Office for examination, and

ultimately allowed by the patent examiner in U.S. Patent Nos. 4,452,808 (the "'808 patent") and 4,824,860 (the "'860 patent") or based on the information in the '808 patent specification concerning human dosage.

10. With respect to the generic claims of the '808 and '860 patents, it is my opinion that their scope is reasonable in light of the patents' specification disclosures and that such claim scope is typical of generic claims that patent practitioners appearing before the United States Patent & Trademark Office routinely seek to protect an invention to a new chemical compound and/or to a method of using that compound. It is a function of a patent attorney or patent agent to seek patent claims as broad as possible in light of the patent application disclosure taking into account input from the inventor(s), the relevant prior art of which he or she is aware, and the conditions for patentability defined in the patent statute, 35 U.S.C § 101, et. seq. It is up to the patent examiner whether to allow or deny any given claim scope. Teva does not appear to challenge the accuracy of the description of the work leading to the inventions of the '808 patent and the '860 patent set forth in the specifications of these two patents. In the absence of the non-disclosure or material misrepresentation of material information, there is no basis for inequitable conduct.

11. With respect to the information in the '808 patent specification concerning human dosage, the plain language of this example indicates that it is a prophetic example. Moreover, a patent examiner would construe it as such in light of the language used and the commonly known fact that nearly all pharmaceutical patents which claim new chemical entities ("NCE") are filed very early before human clinical trials are commenced. It is generally known that clinical trials are begun many years after the

filing of an initial patent application for a NCE. Accordingly, there is no basis for concluding that there was any misrepresentation in the '808 patent with respect to dosage.

QUALIFICATIONS

12. I received a Bachelors of Science degree in Chemistry from Rutgers University in 1959, and a *Juris Doctor*, with Honors, from the George Washington University School of Law in 1963.

13. I was a patent examiner at the United States Patent & Trademark Office from 1959 until 1963. Due to my experience as a patent examiner, I was admitted to practice before the United States Patent & Trademark Office by approximately 1964. During my time as a patent examiner, I was responsible for examining patent applications for small molecule pharmaceuticals and reviewed at least 150 United States patent applications. I received from the Department of Commerce three awards for superior performance during my four-year tenure as a patent examiner.

14. From 1963 until 1971, I was in private practice with Darby & Darby in New York, NY. During my years in private practice, I gained experience in nearly all areas of patent and trademark law, including patent and trademark procurement, opinion writing, client counseling, and intellectual property litigation. During that time, I drafted at least 50 United States patent applications in the chemical arts.

15. In 1971, I joined American Home Products Corporation, which is now known as Wyeth, as a senior patent attorney. In that capacity, I was responsible for filing patent applications, preparing and reviewing intellectual property agreements, and

coordinating with both in-house and outside intellectual property litigation and patent counsel. As a senior patent attorney I drafted at least 40 United States patent applications.

16. In 1974, I was promoted to patent and trademark litigation counsel. My expanded responsibilities included the supervision of company-wide patent and trademark litigation, intellectual property due diligence strategies, and the preparation and review of intellectual property agreements.

17. From 1987 to 2004, I served first as an Assistant General Counsel, and then later as an Associate General Counsel. In 1996, I was promoted to the title of Vice President and Associate General Counsel, Intellectual Property. During this 17-year period, I was responsible for Wyeth's extensive worldwide patent and trademark portfolio, which today includes approximately 2,000 United States patents. As Associate and Assistant General Counsel, I counseled senior management daily regarding intellectual property issues, performed patent infringement and validity analysis, supervised intellectual property litigation, and managed over 30 intellectual property attorneys and agents.

18. I retired from Wyeth on February 1, 2004, and I have consulted for Wyeth and other pharmaceutical companies, including GSK, on a part-time basis since my retirement and continue to do so.

19. I have been a member of professional associations, including the American Bar Association, the Licensing Executives Society, and the American Intellectual Property Association. While employed by Wyeth and since 1987, I

represented the corporation on the Patent Committee of the Pharmaceutical Research and Manufacturers of America (PhRMA), and I was a member of Interpat, an organization composed of chief in-house patent counsel of multinational companies engaged in the research and development of pharmaceutical products.

20. In the past, I have lectured on the interaction of in-house and outside counsel in patent litigation from the perspective of in-house counsel before the American Bar Association, the Practicing Law Institute, the Southwestern Legal Foundation, the New Jersey Patent Law Association, the New York Patent, Trademark and Copyright Association, and at the BNA Annual Patent Conference.

BACKGROUND

21. For the purposes of this report, I have been asked to assume that the facts recited below concerning the circumstances under which the claimed inventions were made are true:

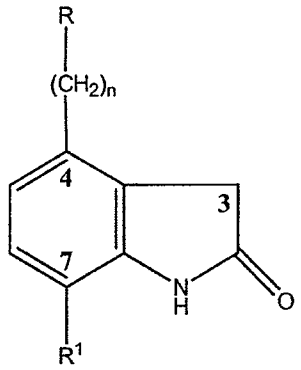
(a) The drug at issue in this case is REQUIP®, which has been used to treat patients suffering from Parkinson's Disease and Restless Legs Syndrome. REQUIP is the commercial name for ropinirole hydrochloride. Two patents relating to this compound are at issue in this litigation. The first, United States Patent No. 4,452,808 (the "'808 patent"), covers the compound itself. The second, United States Patent No. 4,824,860 (the "'860 patent"), covers the use of the compound for the treatment of Parkinson's Disease.

(b) Mr. Gregory Gallagher, a chemist employed at GSK, first synthesized ropinirole. At the time of the invention, Mr. Gallagher was experimenting with a compound described in GSK's U.S. Patent No. 4,314,944 (the "'944 patent") and given the internal designation SK&F 89124 by GSK. Mr. Gallagher synthesized the compound ropinirole by removing the hydroxy (i.e., an oxygen and hydrogen) from the SK&F 89124 compound. Mr. Gallagher sent ropinirole to the GSK pharmacology department to perform routine screening tests to determine whether the compound had cardiovascular utility. Testing by the pharmacology department revealed that ropinirole was a dopamine agonist and exhibited cardiovascular activity. The GSK patent department filed the patent application for ropinirole on December 7, 1982, and a patent was issued on June 5, 1984.

(c) In approximately 1985, responsibility for developing ropinirole was transferred from the GSK Philadelphia offices to the Welwyn offices in the United Kingdom. In the course of performing tests designed to assess the cardiovascular activity of ropinirole, a GSK technician observed stereotypic behavior in rats that had been dosed with ropinirole. This observation led to the discovery by Dr. David Owen, the director of the pharmacology department at Welwyn, that ropinirole could be used for the treatment of Parkinson's Disease. Dr. Owen then retained Professors Brenda Costall and R.J. Naylor of the University of Bradford to perform testing to confirm Dr. Owen's discovery. After Bradford University confirmed Dr. Owen's discovery, Dr. Owen deferred to the GSK patent department to determine the proper scope of the patent application addressing ropinirole's anti-Parkinson's effect. A U.K. patent application was

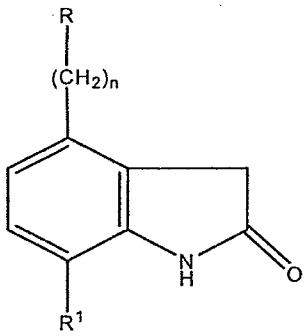
filed on May 21, 1987. The United States patent application, which claims priority to the U.K. application, was filed on May 19, 1988, and the '860 patent issued on April 25, 1989.

22. The '944 patent names William Huffman and James Wilson as inventors and discloses a new group of 2(3H)-indolones whose structures are characterized by a 2(3H)-indolone (oxindole) nucleus having an aminoalkyl substituent at the 4-position and an oxygen function at the 7-position as shown in the generic structure below:



The '944 patent describes two different methods, labeled as Scheme A and Scheme B, by which to synthesize the 2(3H)-indolone compounds disclosed in the patent. The compounds of the '944 patent are described as having beneficial cardiovascular effects and supporting pharmacological data is disclosed for a number of the claimed compounds. The '944 patent also contains six examples. Examples 1, 2, 5, and 6 teach methods of preparing 7-methoxylated 2(3H)-indolones having varying substituents at the 4-position while examples 3 through 6 teach methods of preparing 7-hydroxylated 2(3H)-indolones having varying substituents at the 4-position. Example 1 is a working example while example 6 is a prophetic example. Examples 2 through 5 are combinations of working examples and prophetic examples. Claim 1 of the '944 patent is recited below:

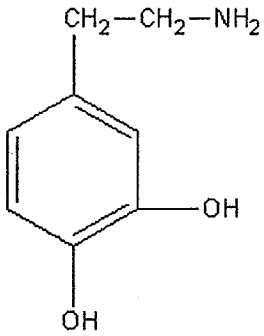
A compound of the structural formula:



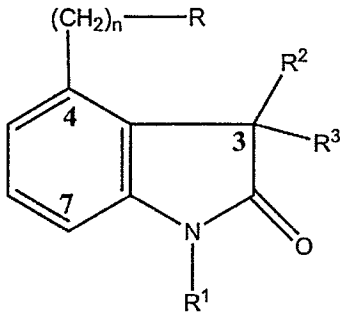
in which R is amino, lower alkylamino, di-loweralkylamino, di-N-allylamino or N-allyl-N-lower alkylamino, R^1 is hydroxy or methoxy and n is an integer from 1-3; together with the pharmaceutically acceptable acid addition salts thereof.

Claims 2 through 9 are directed to compounds with varying substituents at the R and R^1 positions.

23. The '808 patent names Gregory Gallagher, Jr. as the inventor and discloses certain novel 4-aminoalkyl-2(3H)-indolones, which primarily differ from the compounds disclosed in the '944 patent in that they lack a hydroxyl group (or a methoxy group) at the 7-position. The '808 patent describes how the disclosed compounds are dopamine agonists despite the lack of the supposedly essential 7-hydroxy group, a substituent on dopamine which has the structure shown below:

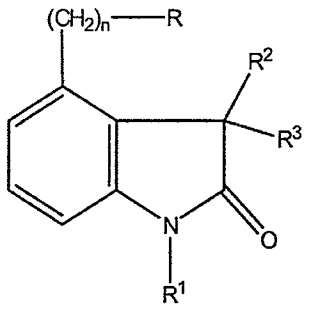


According to the '808 patent disclosure, this 7-hydroxy group was believed necessary for the '944 compounds to resemble the structure of dopamine. The generic chemical structure of the compounds disclosed in the '808 patent is shown below:



The '808 patent describes two different methods, labeled as Scheme A and Scheme B, by which to synthesize the 4-aminoalkyl-2(3H)-indolone compounds disclosed in the '808 patent. The compounds of the '808 patent are disclosed as being peripheral dopamine agonists with beneficial cardiovascular activity as evidenced by supporting pharmacological data for ropinirole hydrochloride, one of the claimed compounds. The '808 patent contains nine examples. Example 1 teaches how to make 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride ("ropinirole hydrochloride") by applying Scheme A while example 2 teaches how to make ropinirole hydrochloride by applying Scheme B. Examples 3 through 8 teach methods of preparing compounds of the patent with various 4-position substituents. Example 8 also teaches methods of preparing compounds with 3-position substituents. Example 9 teaches how to make a ropinirole formulation for administration to patient. Examples 1 and 2 are working examples while examples 3 through 7 and 9 are prophetic examples. Example 8 is a combination of a working example and a prophetic example. Claim 1 of the '808 patent is recited below:

A compound of the structural formula:

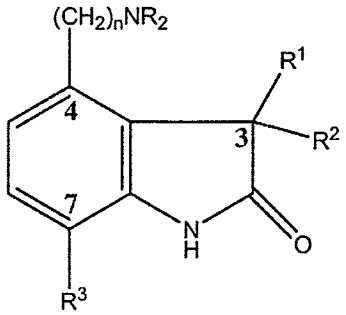


in which: n is 1-3, R is amino, C_{1-6}-lower alkylamino, di-(C_{1-6}-lower alkyl)amino, allylamino, diallylamino, N-(C_{1-6}-lower alkyl)-N-allylamino, benzylamino, dibenzylamino, phenethylamino, diphenethylamino, 4-hydroxyphenethyl amino or di-(4-hydroxyphenethyl)amino, and R^1, R^2 and R^3 are, each, hydrogen or C_{1-4}-lower alkyl; or a pharmaceutically acceptable, acid addition salt thereof.

Claims 2 through 7 are directed to compounds with varying substituents at the R, R^1, R^2, and R^3 positions. Claim 8 is directed to a pharmaceutical composition having D_2 receptor agonist activity comprising a nontoxic, agonist quantity of a compound of the structural formula shown above for claim 1, in dosage unit form, combined with a pharmaceutical carrier. Claims 9 and 10 are directed to the composition of claim 8 in which the D_2-agonist compound is 4-(2-di-n-propylaminoethyl)-2(3H)-indolone or 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride, respectively, while claim 11 is directed to the composition of claim 8 in dosage unit form adapted for use as an antihypertensive composition. Claim 12 is directed to a specific quantity per unit dosage.

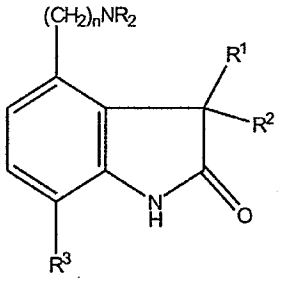
24. The '860 patent lists David Owen as the inventor and claims a method of treatment of Parkinson's Disease by the administration of certain indolone derivatives. The indolone derivatives disclosed in the '860 patent include some of the compounds disclosed in the '944 and '808 patents. The '860 patent discloses the discovery that these

prior art indolone compounds, previously thought to be peripheral dopamine agonists, exhibit central nervous system ("CNS") effects and could be a successful treatment for Parkinson's Disease. The generic chemical structure of the compounds disclosed in the '860 patent is shown below:



There are seven examples (A-G) in the '860 patent. Example A describes the effect of ropinirole hydrochloride, one of the claimed compounds, on spontaneous locomotor activity in mice. The results of this test indicate that ropinirole hydrochloride has dopamine agonist activity. Example B describes the ability of ropinirole hydrochloride to induce stereotypy in rats or mice. The results of this test are indicative of a more selective mode of dopamine agonist action. Example C demonstrates that ropinirole hydrochloride has anti-Parkinson potential based on its effect on locomotor activity in the rat. Example D shows that ropinirole hydrochloride exhibits statistically significant anti-depressant activity based on its effect in the Porsolt Test. Example E demonstrates ropinirole hydrochloride's anxiolytic effects and example F demonstrates the anti-Parkinson activity of ropinirole hydrochloride in the MPTP-Treated Marmoset Model. Example G shows the results of receptor binding studies, demonstrating that ropinirole hydrochloride is more selective in its binding to dopamine receptors than other D_2

agonists, bromocriptine and pergolide. All of the examples in the '860 patent are working examples. Claim 1 of the '860 patent is recited below:

> A method of treatment of Parkinsons Disease which comprises administering an effective non-toxic amount for the treatment of Parkinsons Disease of a compound of the following structure:
>
> 
>
>
> in which each group R is hydrogen or C_{1-4} alkyl;
> R^1 and R^2 are each hydrogen or C_{1-4} alkyl;
> R_3 is hydrogen or hydroxy; and
> n is 1 to 3;
> or a pharmaceutically acceptable salt thereof to a subject in need thereof.

Claims 2 and 3 are directed to a method of treatment of Parkinsons Disease which comprises administering an effective non-toxic amount for the treatment of Parkinsons Disease of 4-(2-di-n-propylaminoethyl)-2-(3H)-indolone or 4-(2-di-n-propylaminoethyl)-2-(3H)-indolone hydrochloride, respectively, to a subject in need thereof.

OPINIONS

I. Teva's Allegations of Inequitable Conduct with Respect to the Generic Claims of the '808 and '860 Patents.

A. The Generic Claims of the '808 Patent

25. Teva has alleged that the '808 patent is invalid because, in addition to ropinirole hydrochloride which is claimed in dependent claim 5, the patent covers several

related compounds in claims 1-4, 6-9, and 11-12, which Mr. Gallagher allegedly did not invent. See Teva Corrected and Amended Counterclaim ¶¶ 34-43. According to Teva, "the applicants' nonjoinder of individual(s) responsible for conceiving of portions of the claimed invention(s) covering compounds other than ropinirole or its hydrochloride salt and Mr. Gallagher's and the applicants' submission of the false declaration of inventorship were done with deceptive intent." Corrected and Amended Counterclaim ¶ 43.

26. Teva's theory of inequitable conduct reflects a fundamental misunderstanding of the claim drafting process and the role of the patent practitioner before the United States Patent & Trademark Office in attempting to obtain patent protection for an invention relating to a pharmaceutical compound. If accepted generally, it would substantially and retroactively curtail the scope of protection available to companies for new and useful compounds and could render numerous patents, including those of Teva, unenforceable.

27. Inventors in a pharmaceutical company, as elsewhere, have varying degrees of familiarity with the patent prosecution process. Inventors are very rarely lawyers or patent agents and therefore naturally rely on the advice and judgment of the lawyers or patent agents responsible for obtaining patent protection for the invention. Among the duties of the patent practitioners before the United States Patent & Trademark Office is the obligation to obtain the broadest claims possible that meet the requirements of Title 35, consistent with the disclosure of the patent application, the scope of the prior art of which he or she is aware, and the duty of candor. Accordingly, prosecuting attorneys are trained to draft and seek to obtain, broad, generic claims, which fairly

reflect the contribution of the inventor to the art. In doing so, they routinely seek and are granted protection beyond the specific embodiment(s) discovered or developed by the inventor. Treatises and written guidance addressing patent drafting confirm that this is the approach that should be followed in drafting genus claims.[1/]

28. With respect to chemical patents in particular, a patent limited to the precise compounds reduced to practice by an inventor would frequently be of little or no value because of the ability to obtain the same functionality of the compound by making minor substituent variations or manipulations to the molecule. Thus, it is normal practice for a patent attorney to draft a patent application to include generic formulas that would include any related substituents that could reasonably be expected to exhibit similar activity and to seek claims to such generic formulas. This does not make the inventor of the chemical compound any less the inventor of the generic formula. Rather, invention of the specific compound entitles the inventor to a genus of compounds of reasonable scope.

[1/] See, e.g., Robert C. Faber, *Landis on Mechanics of Claim Drafting*. § 10:1.1, 5th Ed., 2005 ("Broad coverage means not only that every particular preferred disclosed embodiment is protected in the claims, but that the claims cover all expected and unanticipated equivalents that competitors and others may later develop and all intentional and unintentional copies of the claimed invention which embody the inventor's concept. The inventor/client will compare a competitive or a similarly functioning product or process with the patented embodiments. If the client sees similar structure, operation and/or result, he will want to be able to use his patent to halt an infringement. It is the claim drafter's job to have written the claims in the application to not only cover what the attorney and the inventor/client could at the time of application prosecution have envisioned as competing products, but to cover competitive products which neither the inventor nor the attorney thought of or could even have imagined at the time, but which employ the concept of the invention."); Jeffrey G. Sheldon, *How to Write a Patent Application*, Practicing Law Institute, § 6.5, 2006 ("The broadest claim should be as broad as possible in view of the prior art. As long as the broad claim is not anticipated by art known to the inventor, it cannot hurt to ask for the broad claim. At worst, the examiner will not allow the broadest claims. Thus, it is recommended that the practitioner be greedy when initially writing the application."); Irving Kayton, *Kayton on Patents*, 2nd ed., 3-1, 1983 ("During the prosecution stage the drafter will naturally attempt to write one claim that is as broad as the prior art of which he is aware will permit and that is supported by the disclosure in his patent application.").

29. A genus or generic claim is one that covers more than a single chemical compound. The practice of obtaining generic claims described above is consistent with standard industry practice and basic patent law principles, as I understand them. It is typical for a patent attorney or agent to more broadly claim the invention to include other species that are envisioned to have the same utility and can be similarly made in order to ensure that the invention is protected. This broadened concept becomes the genus in a patent application. Moreover, the existence of only one working example or even the possibility of inoperative species does not automatically result in the genus claim not meeting the statutory requirements. It is acceptable for a specification to merely contain a written description of the broadly claimed invention without having to, in addition, detail every species that is encompassed by such a genus claim.[2/]

30. Based on the facts set forth above and the facts which I have been asked to assume as true, the prosecution of the '808 patent appears to have been entirely consistent with normal patent prosecution practice related to the prosecution of generic chemical claims. Mr. Gallagher was the first and only person to initially synthesize ropinirole, and

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[2/] These standard industry practices have been upheld by the courts as permissible as a matter of law. See, e.g., *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970) (stating that as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied); *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 974 (Fed. Cir. 2002) (Lourie, J., concurring in decision to deny rehearing en banc) ("Although one may envision a general concept, what one usually does first in making or isolating a chemical or chemical-related invention is to obtain a specific material or materials. One then broadens the concept to extend it as far as one envisions that other materials will have the same utility and can be similarly made. That broadened concept becomes the genus in a patent application that is both the broadest statement constituting a written description and usually claim 1."); *Atlas Powder Co. v. E.I. du Pont de Nemours and Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984) (holding that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled); *Utter v. Hiraga*, 845 F.2d 993, 998 (Fed. Cir. 1988) ("A specification may, within the meaning of 35 U.S.C. §112 ¶ 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses.").

it was he who was responsible for sending the compound to GSK's pharmacology department for routine testing as to its utility. Mr. Gallagher apparently did not make any other compounds coming within the scope of claim 1 of the '808 patent, but the application for the '808 patent does not purport to describe any working examples of other compounds. Even assuming Mr. Gallagher did not make such compounds, Teva's counterclaim alleging improper inventorship fails to identify by name any alleged co-inventors.

31. As discussed above, the specification of the '808 patent describes a way to synthesize ropinirole and provides data supporting its utility. The '808 patent also provides several prophetic examples of the synthesis of related compounds other than ropinirole coming within the generic formula. In light of the disclosure of the '808 patent and the disclosure of the '944 patent (which is cited in the '808 patent as prior art), the generic claim sought by the applicant in the '808 patent is most reasonable, and it is not surprising that the examiner allowed it. No objection was made by the examiner that any species within the genus claim of the '808 patent did not have utility. This is consistent with the Manual of Patent Examining Procedure's ("MPEP")[3/] guidance for patent examiners when considering the scope of generic claims:

> With respect to the adequacy of disclosure that a claimed genus possesses an asserted utility representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if it would be deemed likely by one skilled in the art, in view of contemporary knowledge in the art, that the claimed genus would possess the asserted utility. Proof of utility will be required for other members of the claimed genus only in those cases where

[3/] The MPEP is published by the USPTO to provide patent examiners, applicants, attorneys, and those involved in the prosecution of a patent with instruction and reference on the patent prosecution practices and procedures before the USPTO.

> adequate reasons can be advanced by the examiner for believing that the genus as a whole does not possess the asserted utility.

MPEP § 608.01(p) at pp. 102-3 (4th ed., rev. Sep. 1982) (citations omitted).[4/] The patent examiner who examined the '808 patent had before him the genus disclosed in the '944 patent, which had been cited to the PTO by the applicant and which was the closest prior art. Given the disclosure, it would have been reasonable to conclude that the claimed genus of the '808 patent would possess the asserted utility.

32. In considering the issues in this case, I have reviewed several Teva patents to compare them to the '808 patent. Not surprisingly, it appears that Teva has commonly sought and obtained broad generic claims notwithstanding a patent disclosure that describes a relatively small number of closely related species actually made and tested by the inventors relative to the scope of the broadest generic claim. See Attachment C. For example, claims 1 and 7 of Teva's U.S. Patent No. 5,585,358 ("'358 patent"), directed towards derivatives of 2-propylpentanoic acid (valproic acid) and 2-propyl-2-pentenoic acid, have broader genus claims than the '808 patent claims. Claim 1 describes a compound with substituents R_1, R_2, and R_3 "wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is equal to 0," while Claim 7 recites a structure "wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3." The '358 patent describes a broad and varied list of aralkyl and aryl

[4/] The above quote is from the September 1982 revision of the MPEP, which was in effect at the time of the filing of the '808 patent in December 1982. There was another MPEP revision in August 1983, which recites the same language as quoted above. In addition, the MPEP's guidance on the utility of genus claims did not substantively change in its 1988 through 1989 editions which were in effect at the time of the filing and prosecution of the '860 patent.

substituents in column 2, lines 60-68, and in column 3, lines 1-2, with only two working examples to illustrate those broad classes of structurally diverse substituents. Only a single working example appears in the '358 patent to support at least 15 diverse substituents represented by "R_1, R_2, R_3" which are recited in claim 5 of this patent.

33. By way of further example of standard industry practice, the patent underlying the world's best selling drug, Pfizer's Lipitor®, claims a genus that is greater in size and scope than that claimed in the '808 patent. Claim 1 of U.S. Patent No. 4,681,893 (the "'893 patent") designates a wide-ranging scope of possible substituents at positions R_1-R_4, yet only provides four exemplified species. See Attachment D. The patent claims remain valid today, nearly twenty years after issue, despite challenges by generic manufacturers. Most recently, the '893 patent was upheld in *Pfizer, Inc. v. Ranbaxy Labs.*, 06-1179 (Fed. Cir. August 2, 2006), appealed from *Pfizer, Inc. v. Ranbaxy Labs.*, 405 F. Supp. 2d 495 (D. Del. 2005).[5/]

34. To summarize, the prosecution of the '808 patent is consistent with the practice of prosecuting pharmaceutical patents that has been commonplace throughout my career. A patent application was drafted which reflects Mr. Gallagher's actual work and includes prophetic examples, the accuracy of which Teva does not contest.

B. The Generic Claims of the '860 Patent

35. It is also my understanding that Teva attacks the generic claims contained in the '860 patent on similar grounds. Teva asserts that claim 1 of the '860 patent claims indolone compounds other than simply ropinirole or its hydrochloride salt. According to

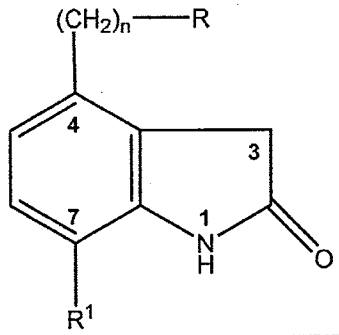
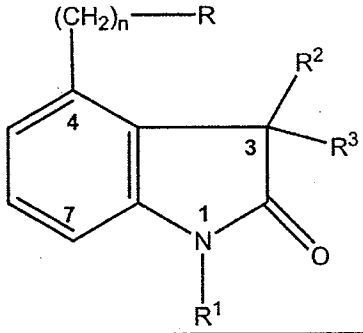
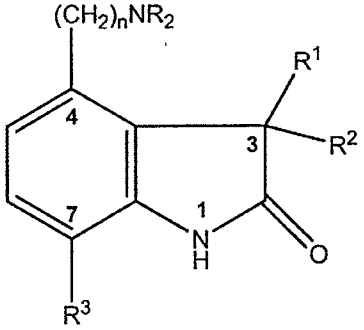
[5/] In fact, based upon both opinions, it does not appear that the validity of the generic claim was even challenged in the lawsuit.

Teva, "[p]laintiffs' nonjoinder of individual(s) responsible for conceiving of portions of the claimed inventions(s) covering compounds other than ropinirole or its hydrochloride salt was done with the intent to deceive the PTO so that the '860 patent would be issued." Corrected Amended Complaint ¶ 60.

36. The '860 patent does not suggest that any compound other than ropinirole had been actually tested for its anti-Parkinson's Disease effect. As with the '808 patent, GSK was nonetheless entitled to a genus claim of appropriate scope. The generic claim of the '860 patent that was sought and obtained by GSK is reasonable in light of the disclosure of the '860 patent and the prior art.

37. Given the teaching of the '944 and '808 patents, it would have been reasonable to seek a genus claim in the '860 patent of substantially the same scope as the '808 patent and the '944 patent. However, the genus in claim 1 of the '860 patent is narrower at the 4-position than the genus claimed in the '944 or '808 patents as shown in the chart below comparing the genus claims of these patents. The genus of claim 1 of the '860 patent is also narrower than the genus of the '808 patent at the 1-position as shown below. In the '860 patent, hydrogen is bound to the indole nitrogen ring, whereas in the '808 patent there may be either hydrogen or a lower-alkyl substituent bound to the indole nitrogen ring.

COMPARISON OF GENUS CLAIMS IN '944, '808, & '860 PATENTS

'944 Patent	'808 Patent	'860 Patent
		
R	**R**	**NR_2**
Amino	Amino	Amino (when both **R**'s = H)
lower alkylamino	C_{1-6} lower alkylamino	C_{1-4} alkylamino (when one **R** = H and the other **R** = C_{1-4}-lower alkyl)
di-loweralkylamino	di-(C_{1-6}-loweralkyl)amino	di-(C_{1-4}-loweralkyl)amino (when both **R**'s = C_{1-4}-lower alkyl)
	allylamino	
di-N-allylamino	diallylamino	
N-allyl-N-lower alkylamino	N-(C_{1-6}-lower alkyl)-N-allylamino	
	benzylamino, dibenzylamino	
	phenethylamino, diphenethylamino	
	4-hydroxyphenethyl amino, di-(4-hydroxyphenethyl)amino	
R^1	**(position not designated)**	**R^3**
Hydroxy (OH)		Hydroxy
Methoxy (OCH_3)		
	Hydrogen	Hydrogen
(position not designated)	**R^1**	**(position not designated)**
Hydrogen	Hydrogen	Hydrogen
	C_{1-4}-lower alkyl	
(position not designated)	**R^2,R^3 (independently)**	**R^1,R^2 (independently)**
Hydrogen	Hydrogen	Hydrogen
	C_{1-4}-lower alkyl	C_{1-4}-lower alkyl
n	**n**	**n**
1-3	1-3	1-3

The fact that GSK drafted narrow genus claims appropriate for each patent reflects a careful and considered approach to prosecuting this family of patents.

38. As with the '808 patent, the prosecution of the genus claim in the '860 patent proceeded in a manner consistent with standard practice in the pharmaceutical industry then and today. Dr. Owen appropriately relied on his patent attorney to obtain a claim of appropriate scope in light of the prior art and the disclosure of the '860 patent. The claim sought by GSK is reasonable but, in any event, it is not inequitable conduct to seek claims as broad as possible taking into account the teachings of the specification and the prior art.

II. The Use of Prophetic Examples Regarding Human Dosing

39. It is my understanding that Teva alleges that the '808 patent is invalid because it asserts that GSK misled the Patent Office into believing that it had already tested for an effective dose in humans. This allegation is unfounded in light of the actual disclosure of the '808 patent.

40. Pharmaceutical patents sometimes include a human dose recommendation. The '808 patent is no different. It states:

> Advantageously, doses selected from the dosage unit ranges given above will be administered several times, such as from one to five times, a day. The daily dosage regimen is selected from the range of about 50 mg to about 1.0 mg, preferably 200-750 mg for oral administration and 50-500 mg for parental administration. When the method described above is carried out, D2-agonist activity is produced.

> For an average size human using 4(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride as an active ingredient, a typical dose to show anti-hypertensive activity would be selected from the range of from about 100-250 mg of base equivalent for each dosage unit which is adapted for oral administration and which is administered orally from 1-4 times daily.

Column 5, line 59 to col. 6, line 5.

41. Based on my experience as a patent attorney and patent examiner, it is my opinion that the above excerpt is a prophetic example. In the drafting of patents, the distinction between actual "working" examples and "prophetic" examples is well established. According to the MPEP, working examples correspond to work actually performed. MPEP § 608.01(p) at 104. However, prophetic examples are also common in patents:

> Simulated or predicted test results and prophetical examples (paper examples) are permitted in patent applications. . . Paper examples describe the manner and process of making an embodiment of the invention which has not actually been conducted.

Id. Working examples typically use the past tense to describe the actual work performed, while "[p]aper examples should not be described using the past tense." *Id.*[6/] Therefore, because of the absence of the use of the past tense throughout the dosing discussion of the '860 patent, a patent examiner would not have interpreted this dosage recommendation as a representation of testing that had already been completed. Indeed, this passage actually employs the future tense as well as the present tense, emphasizing the predictive intent of the statements, including, for example, "doses selected . . . *will be*

[6/] The August 1983 MPEP revision recites the same language with regard to prophetic examples as the September 1982 edition quoted above.

administered[,]" "*[w]hen* the method described above is carried out ...[,]" and "a typical dose to show anti-hypertensive activity *would be* selected . . . ." The future tense is clearly utilized to signal to the patent examiner that this is a prophetic example. It is common for pharmaceutical patents to have prophetic examples, particularly when it comes to dosing recommendations. I note that Teva appears to have employed a prophetic example with regard to the effectiveness of a claimed dose in one of its own pharmaceutical patents.[7/]

42. In addition, as a matter of common sense, a new chemical compound that is the subject of a pharmaceutical patent application would often and most likely not have been actually tested in humans at the time the application was filed. The Hatch-Waxman Act -- the federal statute that is the basis for ANDA filings such as the Teva ANDA at issue in this proceeding -- also provides for patent term extension precisely because of the loss of patent life due to FDA-required human clinical testing. Yet, a pharmaceutical company must file its patent application at an early stage or run the risk that others may publish on the company's compounds and impair future patent rights abroad where jurisdictions follow "a first to file" system. In fact, a patent examiner would understand that the actual results of human testing would typically be available only for a second or third generation improvement for which patent protection is sought to an existing patented compound.[8/]

[7/] For example, see Teva U.S. Patent No. 6,569,459 directed to a method of administration of paclitaxel-plasma protein formulation. See Attachment E. Example 2 of the '459 patent is written in the present tense as contrasted with Example 1,and suggests a protocol for evaluating the claimed method using a mouse experimental model. The example even goes so far as to generate a table listing experimental values that might be expected to result from such an experiment.

[8/] For examples of Teva patents with claims broadly directed toward therapeutic treatment of a "patient" or a "subject" but disclosing only testing in mice and rats, see U.S. Patent Nos. 6,569,459 (see footnote 7) and 5,585,358 (discussed *supra*).

III. TRIAL EXHIBITS

43. I may rely on visual aids and demonstrative exhibits that demonstrate the basis for my opinion. Examples of these visual aids and demonstrative exhibits may include, for example, diagrams of one or more of the compounds claimed, and blow-ups of documents considered or excerpts from this report.

IV. RESERVATION OF RIGHTS

44. My opinions are based upon the information that I have considered to date. I reserve the right to supplement or amend my opinions in response to opinions (including any rebuttal opinions) expressed by Teva's experts by or in light of any additional evidence, testimony, or other information that may be provided to me after the date of this report, including at trial.

Date: September 22, 2006

Egon E. Berg

Egon E. Berg

Berg Report Exhibit A

EGON E. BERG
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PROFESSIONAL EXPERIENCE

1971 – 2004 American Home Products Corporation/Wyeth (Fortune 100 Company)

1996-2004 **Vice President and Associate General Counsel**

1992-1996 **Associate General Counsel**

1987-1992 **Assistant General Counsel**

Responsible for company-wide IP, including extensive worldwide patent and trademark portfolio; daily senior management counseling, infringement and validity analysis; legal review of IP license agreements, IP due diligence strategies and reviews for the acquisition of businesses and products; supervision of IP litigation, including tactics, strategy; management of 80+ IP attorney and administrative support team.

1974-1987 **Litigation Counsel, Patents and Trademarks**

Responsible for corporate-wide patent and trademark litigation; coordination with and supervision of outside counsel; review of legal briefs, strategy for litigation; direct handling of trademark litigation; IP due diligence strategies and reviews for the acquisition of businesses and products; preparation and review of IP agreements.

1971-1974 **Senior Patent Attorney**

Patent application filing and procurement; preparation and review of IP agreements; supervision of and coordination with outside counsel of IP litigation.

1963-1971 **Darby & Darby** (New York City)
Extensive practice in all phases of patent and trademark law, including patent and trademark procurement, opinion writing, client counseling and IP litigation.

1959-1963 **United States Patent & Trademark Office**
Pharmaceutical Group 120, Patent Examiner

BAR ADMISSIONS

New York, District of Columbia, U.S. Supreme Court and CAFC

EDUCATION

BS Chemistry – 1959 Rutgers University
JD - 1963 George Washington University

OTHER PROFESSIONAL ACTIVITIES

Lecturer PLI, Southwest Legal Foundation

Berg Report Exhibit B

DOCUMENTS CONSIDERED BY EGON E. BERG

GSK-REQ011545-GSK-REQ019834

GSK-REQ024778-GSK-REQ024780

GSK-REQ00674-GSK-REQ006749

GSK-REQ013314- GSK-REQ013313

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Deposition Transcript of David Owen, without exhibits, May 26, 2006

Deposition Transcript of Gregory Gallagher, Jr., without exhibits, May 5, 2006

Teva's Motion for Leave to Amend Its Answers, Defenses, and Counterclaims, with exhibits, June 28, 2006

Teva's Third Supplemental Response to Plaintiff's First Interrogatories, June 9, 2006

Expert Report of Dr. Joseph G. Cannon, with attachments, July 10, 2006

Expert Report of Dr. John Paul Long, with attachments, July 10, 2006

Expert Report of Dr. Daniel Tarsy, with attachments, July 10, 2006

Plaintiff's Brief in Opposition to Defendant's Motion for Leave to Amend its Answer, Defenses and Counterclaims, with exhibits, July 13, 2006

Defendant Teva's Corrected Brief In Support of Motion for Leave to Amend its Answer Defenses, and Counterclaims, July 10, 2006

Defendant Teva's Corrected Motion for Leave to amend its Answer, Defenses, and Counterclaims, July 10, 2006

Defendant's Reply Brief in Support of Motion for Leave to Amend its Answer, Defenses and Counterclaims, with exhibits, July 24, 2006

United States Patent No. 6,569,459

United States Patent No. 5,585,358

United States Patent No.4,681,893

United States Patent No.5,576,353

European Patent No. 0113964-B1

European Patent No. 0299602-B1

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Board of Education v. American Bioscience, Inc., 333 F. 3d 1330 (Fed. Cir. 2003)

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Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc., 326 F.3d 1226 (Fed. Cir. 2003)

Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd., 394 F.3d 1348 (Fed. Cir. 2005)

Burlington Indus., Inc. v. Dayco Corp., 849 F.2d 1418 (Fed. Cir. 1988)

Burroughs Wellcome Co. v. Barr Labs., Inc., 40 F.3d 1223 (Fed. Cir. 1994).

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Critikon, Inc. v. Becton Dickinson Vascular Access, Inc., 120 F.3d 1253 (Fed. Cir. 1997).

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In re Edwards, 568 F.2d 1349, 1351-2 (CCPA 1978)

Enzo Biochem, Inc v. Gen-Probe Inc., 323 F.3d 956 (Fed. Cir. 2002)

Ferring B.V. v. Barr Laboratories, Inc., 437 F.3d 1181 (Fed. Cir. 2006)

Fina Oil & Chemical Co. v. Ewen, , 123 F.3d 1466 (Fed. Cir. 1997)

In re Fisher, 427 F.2d 833 (CCPA 1970)

Ex parte Forman et al., 230 USPQ 546 (BPAI 1986)

Frazier v. Roessel Cine Photo Tech., Inc., 417 F.3d 1230 (Fed. Cir. 2005)

Fujikawa v. Wattanasin, 93 F.3d 1559 (Fed. Cir. 1996)

Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361 (Fed. Cir. 1997)

GFI, Inc. v. Franklin Corp., 265 F.3d 1268 (Fed. Cir. 2001)

Hess v. Advanced Cardiovascular Sys., Inc., 106 F.3d 976 (Fed. Cir.)

Kingsdown Med. Consultants, Ltd., v. Hollister, Inc, 863 F.2d 867 (Fed. Cir. 1988)

In re Marzocchi, 439 F.2d 220 (CCPA 1971)

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Novo Nordisk Pharms., Inc. v. Bio-Technology General Corp., 424 F.3d 1347 (Fed. Cir. 2005)

Oka v. Youssefyeh, 849 F.2d 581 (Fed. Cir. 1988)

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PerSeptive Biosystems v. Pharmacia Biotech, 225 F.3d 1315 (Fed. Cir. 2000)

Pfizer, Inc v. Ranbaxy Labs, 06-1179 (Fed. Cir. August 2, 2006)

Pfizer, Inc v. Ranbaxy Labs, 405 F. Supp. 2d 495 (D.Del. 2005)

Pharmacia Corp. v. Par Pharmaceutical, Inc., 417 F.3d 1369 (Fed. Cir. 2005)

In re Rainer et al., 377 F.2d 1006 (CCPA 1967)

Refac International, Ltd. v. Lotus Development Corp., 81 F.3d 1576 (Fed. Cir. 1996)

Semiconductor Energy Lab. Co. v. Samsung Elecs. Co., 204 F.3d 1368 (Fed. Cir. 2000)

Sewall v. Walters, 21 F.3d 411 (Fed. Cir. 1994).

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In re Ruschig (379 F.2d 990, CCPA 1967)

Utter v. Hiraga, 845 F.2d 993 (Fed. Cir. 1988)

In re Vaeck, 947 F. 2d 488 (Fed. Cir. 1991)

In re Wands, 858 F.2d 731 (Fed. Cir. 1988)

In re Wright, 999 F.2d 1557 (Fed. Cir. 1993)

MPEP § 608.01 (p) 4th ed., rev. 9 Sept. (1982)

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MPEP § 608.01 (p) 5th ed., rev. Oct. (1987)

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MPEP § 608.01 (p) 5th ed., rev. 9 Sept. (1988)

MPEP § 608.01 (p) 5th ed., rev. Jan. (1989)

MPEP § 608.01 (p) 5th ed., rev. Apr. (1989)

Berg Report Exhibit C

US005585358A

United States Patent [19]

Bialer et al.

[11] Patent Number: 5,585,358

[45] Date of Patent: Dec. 17, 1996

[54] **DERIVATIVES OF VALPROIC ACID AMIDES AND 2-VALPROENOIC ACID AMIDES, METHOD OF MAKING AND USE THEREOF AS ANTICONVULSANT AGENTS**

[75] Inventors: **Meir Bialer**, Jerusalem; **Salim Hadad**, Kfar Peki'in; **Jacob Herzig**, Ra'anana; **Jeff Sterling**, Jerusalem; **David Lerner**, Jerusalem; **Mitchell Shirvan**, Jerusalem, all of Israel

[73] Assignees: **Yissum Research Development Corporation of the Hebrew University of Jerusalem**; **Teva Pharmaceutical Industries Ltd.**, both of Jerusalem, Israel

[21] Appl. No.: **88,074**

[22] Filed: **Jul. 6, 1993**

[51] **Int. Cl.**[6] **C07K 5/067**; A61K 38/05

[52] **U.S. Cl.** **514/19**; 564/155; 564/159

[58] **Field of Search** 564/155, 159; 514/19

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,639,468 1/1987 Roncucci et al. .

FOREIGN PATENT DOCUMENTS

0046707 3/1982 European Pat. Off. .
0250997 1/1988 European Pat. Off. .
0442012 8/1991 European Pat. Off. .

OTHER PUBLICATIONS

Granneman, Xenobiotica 14 (5)375(1984).
Yu, Mol. & Chem Neuropath 15, 37 (1991).
Chemical Abstracts 101 (17), 143458v, 1984.
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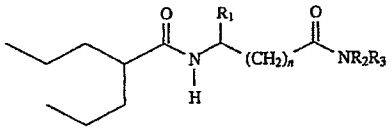
Drugs of the Future 16(8):775 (1991).
Haj–Yehia, A., et al., *Pharmaceutical Research* 6(8):683–689.
Bialer, M., et al., *Eur. J. Clin. Pharmacol.* 38:289–291 (1990).
Bialer, M., *Clin. Pharmacokinet.* 20(2):114–122 (1991).
Hadad, S., et al., *Journal of Pharmaceutical Sciences* 81(10):1047–1050 (1992).

Primary Examiner—Robert Gerstl
Attorney, Agent, or Firm—John P. White

[57] **ABSTRACT**

A compound having the structure:



wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1–C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3. Also provided are a compound containing a 2-valproenoic moiety, pharmaceutical compositions comprising these compounds, and methods of using them for the effective treatment of epilepsy and other neurological disorders.

19 Claims, 2 Drawing Sheets

FIGURE 1

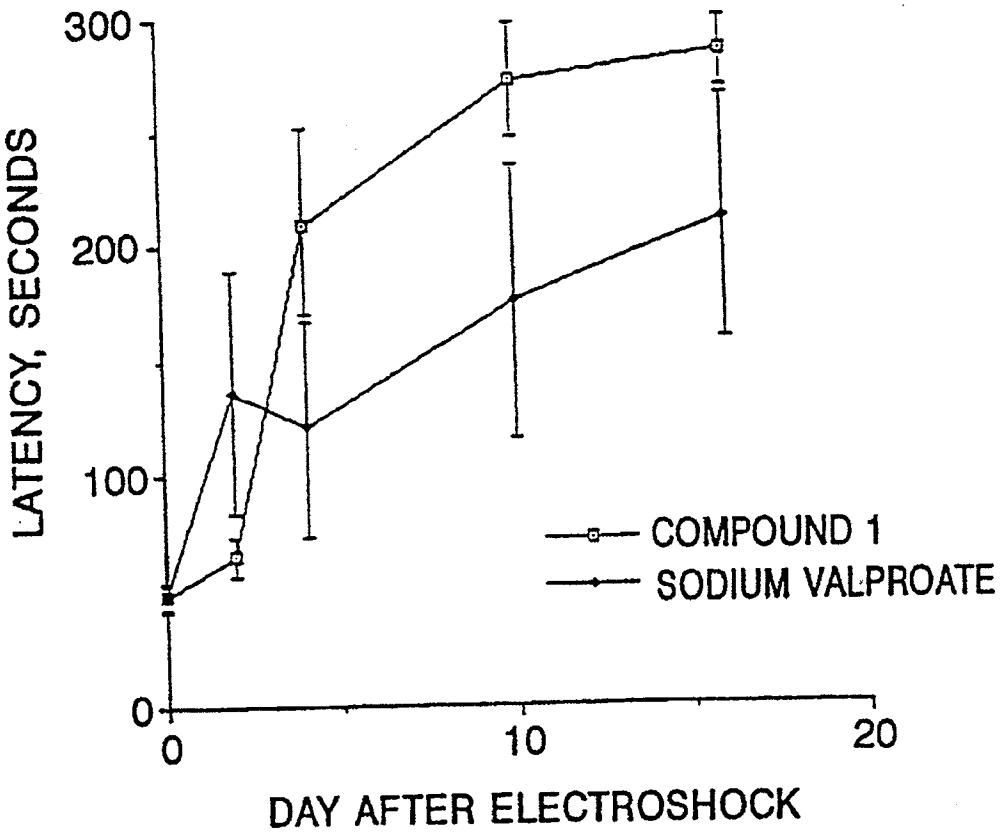
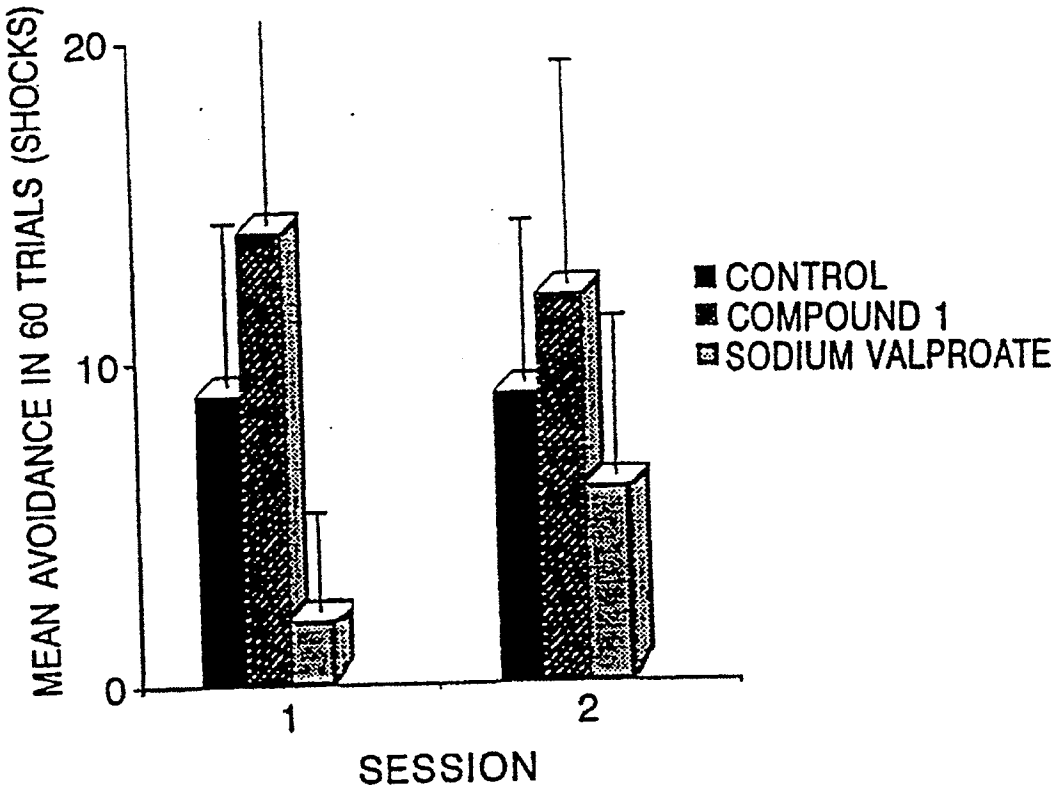

300
200
100
0
LATENCY, SECONDS
0
10
20
DAY AFTER ELECTROSHOCK
COMPOUND 1
SODIUM VALPROATE

FIGURE 2


MEAN AVOIDANCE IN 60 TRIALS (SHOCKS)
20
10
0
1
2
SESSION
CONTROL
COMPOUND 1
SODIUM VALPROATE

DERIVATIVES OF VALPROIC ACID AMIDES AND 2-VALPROENOIC ACID AMIDES, METHOD OF MAKING AND USE THEREOF AS ANTICONVULSANT AGENTS

BACKGROUND OF THE INVENTION

The invention relates to new derivatives of 2-propylpentanoic acid (valproic acid, hereinafter VPA), and 2-propyl-2-pentenoic acid, their preparation and use as antiepileptic agents.

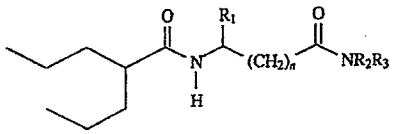
VPA and its alkali salts are major drugs in the arsenal of drugs for the treatment of epileptic seizures and convulsions. However, approximately 25% of epileptic patients do not respond to current treatment. Furthermore, VPA itself has considerable adverse effects including hepatotoxicity and teratogenicity. Baille, T. A. and A. W. Rettenmeier, in "Antiepileptic Drugs," ed. by R. H. Levy, F. E. Dreifuss, R. H. Mattson, B. S. Meldrum and J. K. Penry, Raven Press, New York (1989), at 601–619.

One approach to obtain improved antiepileptic agents has been to prepare the primary amide derivatives of VPA and its analogs. M. Bialer, *Clin. Pharmacokinet.* 20:114–122 (1991); M. Bialer, A. Haj-Yehia, N. Barzaghi, F. Pisani, and E. Perucca, *Eur. J. Clin. Pharmacol.*, 289–291 (1990); A. Haj-Yehia and M. Bialer, *J. Pharm. Sci.*, 79: 719–724 (1990). While certain glycinamide derivatives have been disclosed by R. Roncucci, et al., U.S. Pat. No. 4,639,468, issued Jan. 27, 1987, these compounds generally have not been accepted into clinical practice. Thus, an urgent need still exists in the art for developing anti-convulsant agents with improved efficacy and a wider margin between the dose which is therapeutic and that which is neurotoxic.

VPA and 2-ene-VPA-related glycine amides have been disclosed by Granneman, et al., *Xenobiotica*, 14, 375 (1984), to be minor metabolites of VPA. However, an examination of the mass spectral data therein shows that those compounds are in fact VPA and 2-ene-VPA glycine and cannot be glycinamide conjugates, wherein the glycine nitrogen moiety is attached to the VPA or 2-ene-VPA carbonyl. While Granneman, et al., described these compounds as glycine conjugates, they erroneously named them as VPA and 2-ene-VPA glycinamides, rather than valproyl and 2-ene-valproyl glycine; the latter names are in accord with the method of preparation and the mass spectral data reported by Granneman, et al.

SUMMARY OF INVENTION

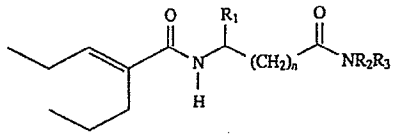
One object of the present invention is to provide a compound having the structure:



I

wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1–C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3.

Another object of the invention is to provide a compound having the structure:



II

wherein R_1 , R_2 , and R_3 are independently the same or different and are hydrogen, a C_1–C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3.

BRIEF DESCRIPTION OF THE DRAWINGS

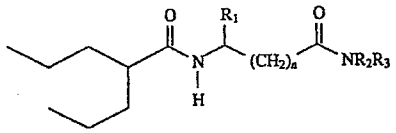
A more complete understanding of the invention and many of its advantages will become apparent by reference to the detailed description which follows when considered in conjunction with the accompanying figures wherein:

FIG. 1 illustrates performance in the passive avoidance test of rats treated with the indicated drugs for the duration of 28 days at the following daily oral doses: Compound 1, 200 mg/kg; VPA, 500 mg/kg. Tests were performed on day 10 after drug treatment. Latency, in seconds, represents response time to entry into dark compartment. Maximum latency is 300 sec. Longer latencies represent improved performance. Bars represent mean standard error (SEM).

FIG. 2 illustrates performance in the active avoidance test of rats treated with the indicated drugs for the duration of 28 days at the following daily oral doses: Compound 1, 200 mg/kg, VPA, 500 mg/kg. Test was performed on days 16–17 (session 1) and 22–23 (session 2) after initiation of drug treatment. Better performance is indicated by an increase in avoidance score, a decrease in latency time, and an increase in the number of crossings.

DESCRIPTION OF THE INVENTION

Compounds of particularly high activity and low toxicity result from the coupling of VPA at the carboxyl group with amino acid amides, and have the general structure I. The present invention provides a compound having the structure:



I

wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1–C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3.

In one embodiment, the invention provides the compound of formula I hereinabove shown wherein the C_1–C_6 alkyl group is a linear chain alkyl group. In another embodiment, the invention provides the compound of formula I hereinabove shown wherein the C_1–C_6 alkyl group is a branched chain alkyl group. In yet another embodiment, the invention provides the compound of formula I hereinabove shown wherein the aralkyl group is a benzyl, alkylbenzyl, hydroxybenzyl, alkoxycarbonylbenzyl, aryloxycarbonylbenzyl, carboxybenzyl, nitrobenzyl, cyanobenzyl, or halobenzyl group. In still another embodiment, the invention provides the compound of formula I wherein the aryl group is a phenyl, naphthyl, anthracenyl, pyridinyl, indolyl, furanyl, alkylphenyl, hydroxyphenyl, alkoxycarbonylphenyl, aryloxycarbon-

ylphenyl, nitrophenyl, cyanophenyl, halophenyl group, mercaptophenyl, or aminophenyl group.

In preferred embodiments, examples of the compound according to the invention include:

N-(2-n-propylpentanoyl)glycinamide;

N-(2-n-propylpentanoyl)glycine-N'-methylamide;

N-(2-n-propylpentanoyl)glycine-N'-butylamide;

N-(2-n-propylpentanoyl)leucinamide;

N-(2-n-propylpentanoyl)alanine-N'-benzylamide;

N-(2-n-propylpentanoyl)alaninamide;

N-(2-n-propylpentanoyl)-2-phenylglycinamide;

N-(2-n-propylpentanoyl)-4-aminobutyramide;

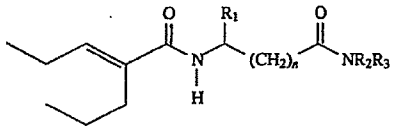
N-(2-n-propylpentanoyl)-β-alaninamide;

N-(2-n-propylpentanoyl)threoninamide; and

N-(2-n-propylpentanoyl)glycine-N',N'-dimethylamide.

In addition, novel compounds having the general structure II exhibiting high activity and low toxicity are related to those having general structure I, except for having a double bond in the 2-position.

The invention therefore provides a compound having the structure:



II

wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1–C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3.

In one embodiment, the invention provides the compound of formula II hereinabove shown wherein the C_1–C_6 alkyl group is a linear chain alkyl group. In another embodiment, the invention provides the compound of formula II hereinabove shown wherein the C_1–C_6 alkyl group is a branched chain alkyl group. In still another embodiment, the invention provides the compound of formula II hereinabove shown wherein the aralkyl group is a benzyl, alkylbenzyl, hydroxybenzyl, alkoxycarbonylbenzyl, aryloxycarbonylbenzyl, carboxybenzyl, nitrobenzyl, cyanobenzyl, or halobenzyl group. In yet another embodiment, the invention provides the compound of formula II hereinabove shown wherein the aryl group is a phenyl, naphthyl, anthracenyl, pyridinyl, indolyl, furanyl, alkylphenyl, hydroxyphenyl, alkoxycarbonylphenyl, aryloxycarbonylphenyl, nitrophenyl, cyanophenyl, halophenyl group, mercaptophenyl, or aminophenyl group.

In preferred embodiments, examples of the compound of formula I according to the invention include:

N-(2-n-propylpent-2-enoyl)glycinamide;

N-(2-n-propylpent-2-enoyl)alaninamide; and

N-(2-n-propylpent-2-enoyl)glycine-N'-methylamide.

The invention further provides a pharmaceutical composition which comprises any compound hereinabove shown in a therapeutically effective amount and a pharmaceutically acceptable carrier. The invention provides a pharmaceutical composition wherein the therapeutically effective amount is an amount from about 10 to about 500 mg. The invention encompasses a pharmaceutical composition as hereinabove described wherein the carrier is a solid and the composition is a tablet. The invention also encompasses a pharmaceutical composition as hereinabove described wherein the carrier is a gel and the composition is a suppository. The invention further encompasses a pharmaceutical composition as hereinabove described wherein the carrier is a liquid and the composition is a solution.

The invention provides a method of treating a subject afflicted with epilepsy which comprises administering to the subject an amount of the compound according to the invention effective to treat epilepsy in the subject.

The invention also provides a method of treating a subject afflicted with affective illness which comprises administering to the subject an amount of the compound according to the invention effective to treat the affective illness in the subject.

The invention additionally provides a method of treating a subject afflicted with cognitive disorders which comprises administering to the subject an amount of the compound according to the invention effective to treat cognitive disorders in the subject.

The invention further provides a method of treating a subject afflicted with neurodegenerative disease which comprises administering to the subject an amount of the compound according to the invention effective to treat neurodegenerative disease in the subject.

The invention also provides a method of treating a subject afflicted with dyskinesiae which comprises administering to the subject an amount of the compound according to the invention effective to treat dyskinesiae in the subject.

The invention still further provides a method of treating a subject afflicted with neurotoxic injury which comprises administering to the subject an amount of the compound according to the invention effective to treat neurotoxic injury in the subject.

The invention provides a method of alleviating convulsions in a subject afflicted with epilepsy which comprises administering to the subject an amount of the compound according to the invention effective to alleviate convulsions in the subject.

The invention also provides a method of treating a subject afflicted with stroke which comprises administering to the subject an amount of the compound according to the invention effective to treat stroke in the subject.

The invention additionally provides a method of treating a subject afflicted with brain ischemia which comprises administering to the subject an amount of the compound according to the invention effective to treat brain ischemia in the subject.

The invention still further provides a method of treating a subject afflicted with head trauma injury which comprises administering to the subject an amount of the compound according to the invention effective to treat head trauma injury in the subject.

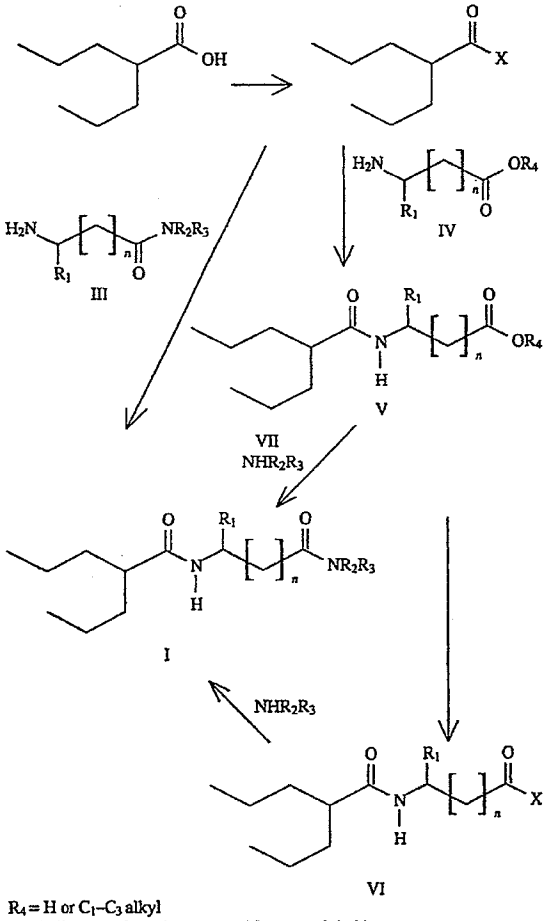
The compounds of general formulas I and II are potent anticonvulsant agents in conventional models of human epilepsy. Several of the compounds have a surprisingly better therapeutic profile than milacemide, VPA, VPA amide analogs or N-valproyl glycine. Furthermore, they may also be useful in the treatment of other CNS dysfunctions.

Suprisingly, the compounds of the invention are highly effective in the MES (maximal electroshock), electrical kindling model, and scMet (subcutaneous pentylenetetrazol) tests. The median effective doses (ED_{50}) of the agents claimed herein are considerably lower than those required to produce neurological impairment.

Therefore, results in animal models distinguish the compounds of the present invention from other antiepileptic agents and indicate that some of the disclosed compounds are effective against generalized and partial seizures, in addition to other forms of epilepsy, including absence seizures.

Some of the compounds of this invention possess chiral centers. It is a further embodiment of this invention that these compounds may comprise substantially pure D or L enantiomers or racemic mixtures. It is to be understood that compounds of the general formula II may be of the E-(trans) or Z-(cis) geometric configuration, or a mixture thereof.

The compounds of general formula I are diamides of valproic acid and may be prepared via conventional amidation processes, e.g., by reacting an activated form of the aforementioned acid either with an amino acid amide of the general formula III, where R_1, R_2, R_3 are the same or different and may be a hydrogen, an alkyl group (C_1–C_6), an aralkyl group or aryl group, and n=0 to 3, or with an amino acid derivative of the general formula IV, in which R_1 and n are the same as for III, and R_4 is hydrogen or a C_1–C_3 alkyl group. The resultant valproyl amino acid derivative V (wherein R_4 is a lower alkyl group) is reacted with amines of the general formula VII, or first activated (wherein R_4 is hydrogen), and the activated form of the acid, VI, is then reacted with VII.



R_4 = H or C_1–C_3 alkyl
X = halide or activated ester, e.g., N-oxysuccinimide

Thus, compounds I and V may be prepared in a biphasic system consisting of a basic aqueous solution of amino acid amides III or amino acid esters IV and a solution of valproyl chloride in an inert water-immiscible organic solvent, e.g. dichloromethane or toluene, at a temperature ranging between 0° and 50° C., preferably at 0°–10° C., for a period of 1 to 24 hrs, preferably 1 to 5 hrs.

The basic substance employed for the purpose may be either alkali, such as sodium hydroxide, potassium hydroxide, or potassium carbonate, or an aliphatic or aromatic tertiary amine, preferably triethylamine, and must be present in a quantity sufficient to neutralize the hydrohalic acid formed during the reaction.

Compounds I and V may also be prepared by reacting an activated ester of VPA with amino acid amides III or amino acid ester IV. Thus, VPA is reacted with an activating agent, e.g., N-hydroxysuccinimide, pentafluorophenol, pentachlorophenol, or 1-hydroxybenzotriazole, in the presence of a dehydrating reagent such as a dialkylcarbodiimide, e.g., dicyclohexylcarbodiimide, diisopropylcarbodiimide, or N-(dimethylaminopropyl)-N'-ethylcarbodiimide, at a temperature ranging from 0°–50° C., preferably at 0°–25° C., in an inert solvent, such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, dichloromethane, or N,N-dimethylformamide. The resulting activated ester may be isolated and purified, or used directly in situ. The activated ester, whether purified or used directly, is reacted with III or IV, under the same conditions leading to condensation as detailed hereinabove.

The reaction of compounds V with amines R_2R_3NH may be carried out in a wide variety of organic solvents, including in an aprotic solvent which is a saturated or aromatic hydrocarbon, such as hexane, benzene, or petroleum ether, or a halogenated solvent, such as chloroform or dichloromethane, in a protic or alcoholic solvent, such as methanol or ethanol, or water. Preferably, the solvent is methanol. The reaction proceeds effectively at a temperature ranging from ambient to reflux, but preferably at 50°–70° C.

Compounds III may be used either as free bases or as their addition salts, formed by treatment of the free bases with an inorganic acid, such as tetrafluoroboric acid, hydrochloric acid, phosphoric acid, or sulfuric acid, or with an organic acid, such p-toluenesulfonic acid, acetic acid, or benzoic acid. Compounds III may be either a pure enantiomeric form, whether of D or L configuration, or a racemic mixture.

The amino acid amides and esters of general formulas III and IV are either commercially available or, alternatively, prepared from appropriate precursors, as detailed in the following examples.

The compounds of general formula II are diamides of valproenoic acid and may be prepared from the latter analogously to the compuonds of the general formula I.

Valproenic acid [(E)-2-ene valproic acid] may be prepared according to procedures known in the art. G. Taillandier, et al., *Arch. Pharm.* (Weinheim), 310, 394 (1977); C. V. Vorhees, et al., *Teratology*, 43, 583 (1991); R. C. Neuman, Jr., and G. D. Holmes, *J. Amer. Chem. Soc.*, 93, 4242 (1971).

In the practice of the invention, the amount of the compound incorporated in the pharmaceutical composition may vary widely. Factors considered when determining the precise amount are well known to those skilled in the art. Examples of such factors include, but are not limited to, the subject being treated, the specific pharmaceutical carrier, and route of administration being employed and the frequency with which the composition is to be administered. A pharmaceutical composition in unit dose form for treatment of the disorders listed hereinabove comprises 10 to 500 mg of the active ingredient.

In a preferred embodiment, the compound is administered in a pharmaceutical composition which comprises the compound and a pharmaceutically acceptable carrier. As used herein, the term "pharmaceutically acceptable carrier" encompasses any of the standard pharmaceutically accepted carriers, such as a phosphate-buffered saline solution, water, emulsions such as an oil/water emulsion or a triglyceride emulsion, various types of wetting agents, tablets, coated

tablets, and capsules. An example of an acceptalbe triglyceride emulsion useful in the intravenous and intraperitoneal administration of the compounds is the triglyceride emulsion commercially known as Intralipid®.

Typically, such carriers contain excipients such as starch, milk, sugar, certain types of clay, gelatin, stearic acid, talc, vegetable fats or oils, gums, glycols, or other known excipients. Such carriers may also include flavor and color additives or other ingredients.

In the practice of the invention, the administration of the pharmaceutical composition may be effected by any of the well known methods including, but not limited to, oral, intravenous, intraperitoneal, intramuscular or subcutaneous or topical administration. Topical administration can be effected by any method commonly known to those skilled in the art and include, but are not limited to, incorporation of the pharmaceutical composition into creams, ointments, or transdermal patches.

The following Experimental Details are set forth to aid in an understanding of the invention, and are not intended, and should not be construed, to limit in any way the invention set forth in the claims which follow thereafter.

EXAMPLE 1

N-(2-n-Propylpentanoyl)glycinamide (compound 1).

A solution of valproyl chloride (108 g, 0.66 mole) in CH_2Cl_2 (500 ml) was added dropwise to an ice-cooled solution of glycinamide. HCl (72 g, 0.65 mole), and Et_3N (138 g, 1.37 mole) in water (200 ml). Cooling was discontinued and the two-phase mixture was stirred at RT for 3 hrs, cooled to 5°–8° C., and acidified to pH 2 by means of 1N HCl. The solid was collected by filtration, slurried in water (300 ml), filtered, dried and crystallized from EtOAc, affording 75 g (0.375 mole, 50%) of the title compound as a white crystalline solid, mp 127° C.

Anal. calc. for $C_{10}H_{20}N_2O_2$: C, 59.97; H, 10.06 N, 13.99; Found: C, 60.09; H, 10.25; N, 14.00.

^{1}H NMR δ ($CDCl_3$): 6.72 (br s, 1H, $CONH_2$), 6.65 (br t, 1H, CONH), 5.75 (br s, 1H, $CONH_2$), 3.98 (d, 2H, gly CαH$_2$), 2.18 (m, 1H, Pr_2CH), 1.57, 1.40 (m, 4H, CH_3CH_2 CH_2), 1.29 (m, 4H, $CH_3CH_2CH_2$), 0.89 (t, 6H, CH_3) ppm.

MS: 201 (MH^+, 100), 184 (MH^+–NH_3, 24).

IR: 3240, 3312, 3181, 2953, 2932, 2872, 1676, 1630, 1549, 431, 1325, 1271, 1221 cm^{-1}

EXAMPLE 2

N-(2-n-Propylpentanoyl)leucinamide.

The title compound was prepared from valproyl chloride (2.0 g, 12.3 mmole) and DL-leucinamide hydrochloride (2.0 g, 12.05 mmole), according to the procedure described in Ex. 1. 2.36 g (9.2 mmole, 76%) of a white crystalline solid, mp 151°–2° C., was thus obtained.

Anal. calc. for $C_{14}H_{28}N_2O_2$: C, 65.58; H, 11.01; N, 10.93; Found: C, 65.28; H, 10.89; N, 10.86.

^{1}H NMR δ (DMSO): 7.85 (br d, 1H, CONH), 7.20 (br s, 1H, $CONH_2$), 6.89 (br s, 1H, $CONH_2$), 4.27 (m, 1H, leu CαH), 2.25 (m, 1H, Pr_2CH), 1.60, 1.42, 1.20 (m, 11H, CH_3 CH_2CH_2, Me_2CHCH_2), 0.88 (d, 3H, leu Me), 0.83 (d, 3H, leu Me), 0.83 (br t, 6H, Me) ppm.

MS: 257 (MH+, 100), 240 (MH^+–NH_3, 32).

IR: 3410, 3300, 2955, 2925, 1720, 1655, 1645, 1540, 1260 cm^{-1}.

EXAMPLE 3

N-(2-n-propylpentanoyl)-2-phenylglycinamide.

A solution of valproyl chloride (1.95 g, 12 mmole) in 1,2-dimethoxyethane (DME, 30 ml) was added to an ice-cooled suspension of phenylglycinamide (1.80 g, 12 mmole, prepared from DL-phenylglycinonitrile, Ger. off. 2637204) and Et3N (2.4 g, 24 mmole) in DME (35 ml). The reaction mixture was stirred under a nitrogen atmosphere for 24 hrs at RT, and the resultant product was collected by filtration, washed with cold hexane (50 ml) and taken into EtOAc/H20 (200 ml:175 ml). The organic layer was separated, washed successively with satd. NaHC03, 0.1N HCl and satd. NaCl, dried and evaporated to dryness. The crude product was crystallized from EtOAc, affording 2.50 g (9.06 mmole, 75%) of the title compound as a white crystalline solid, mp 190°–1° C.

Anal. calc. for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14; Found: C, 68.26; H, 8.57; N, 9.96.

^{1}H NMR δ (DMSO): 8.36 (br d, 1H, CONH), 7.65 (br s, 1H, CONH), 7.46–7.22 (m, 5H, Ph), 7.10 (br s, 1H, $CONH_2$), 5.46 (d, 1H, Ph—CH), 2.44 (m, 1H, Pr_2CH), 1.40, 1.22, 1.10 (m, 8H, $CH_3CH_2CH_2$), 0.85 (t, 3H, Me), 0.78 (t, 3H, Me) ppm.

MS: 277 (MH^+, 56), 201 (100).

IR: 3400, 3300, 2950, 2910, 1735, 1685, 1560, 1400 cm^{-1}.

EXAMPLE 4

N-(2-n-Propylpentanoyl)alanine methyl ester.

A solution of DL-alanine methyl ester hydrochloride (13.7 g, 98 mmole) and Et_3N (20.2 g, 200 mmole) in water (50 ml) was added dropwise to an ice-cooled solution of valproyl chloride (15.0 g, 92 mmole) in CH_2Cl_2 (150 ml). After completion of addition the reaction mixture was stirred for 4 hrs. at RT. The layers were then separated and the aqueous layer extracted with CH_2Cl_2. The combined organic phases were washed successively with water, satd. $NaHCO_3$, 0.1N HCl and satd. NaCl, dried and evaporated to dryness. The residue was treated with hexane (60 ml), and the resultant solid was collected by filtration, washed with hexane and dried to give 14.2 g (62 mmole, 63%) of the title compound as a white solid, mp 72°–3° C.

^{1}H NMR δ ($CDCl_3$): 6.02 (br d, 1H, NH), 4.63 (quintet, 1H, ala CαH), 3.75 (s, 3H, OMe), 2.08 (m, 1H, Pr_2CH), 1.6, 1.4, 1.32 (m, 8H, $CH_3CH_2CH_2$), 1.40 (d, 3H, ala Me), 0.89 (t, 6H, Me) ppm.

MS: 230 (MH^+, 100), 127 (7), 104 (16).

IR: 3300, 2925, 1740, 1630, 1540 cm^{-1}.

EXAMPLE 5

N-(2-n-Propylpentanoyl)glycine methyl ester.

The title compound was prepared from valproyl chloride (19.34 g, 119 mmole) and glycine methyl ester hydrochloride (15.0 g, 119 mmole), according to the procedure described in Ex. 4.22 g (102 mmole, 86%) of an off-white solid, mp 68° C., was thus obtained.

^{1}H NMR δ ($CDCl_3$): 5.97 (br t, 1H, NH), 4.06 (d, 2H, gly CH_2), 3.76 (s, 3H, OMe), 2.14 (m, 1H, Pr_2CH), 1.60, 1.45–1.25 (m, 8H, $CH_3CH_2CH_2$), 0.90 (t, 6H, Me) ppm.

MS: 216 (MH^+, 100), 127 (13).

IR: 3300, 2945, 2920, 1765, 1650, 1550, 1220 cm^{-1}.

EXAMPLE 6

N-(2-n-Propylpentanoyl)alaninamide.

Aqueous ammonia (25%, 50 ml) was added dropwise to a solution of N-(2-propylpentanoyl)alanine methyl ester (6.87 g, 30 mmole) in methanol (20 ml), and the reaction

mixture was stirred under reflux for 4 hrs. The solid which precipitated upon cooling was filtered, washed with cold hexane, dried and crystallized from EtOAc to give 1.90 g (8.92 mmole, 30%) of the title compound as a white crystalline solid, mp 165°–166° C.

Anal calc. for $C_{11}H_{22}N_2O_2$: C, 61.64; H, 10.35; N, 13.08; Found: C, 61.35; H, 10.26; N, 13.32.

^{1}H NMR δ (DMSO): 7.84 (br d, 1H, CONH), 7.21 (br s, 1H, $CONH_2$), 6.92 (br s, 1H, $CONH_2$), 4.25 (quintet, 1H, ala CαH), 2.24 (m, 1H, Pr_2—CH), 1.42, 1.20 (m, 8H, $CH_3CH_2CH_2$), 1.17 (d, 3H, ala Me), 0.833 (t, 3H, Me), 0.827 (t, 3H, Me) ppm.

MS: 214 (M^+,1), 170 (M^+–$CONH_2$, 100).

IR: 3390, 3295, 1675, 1620 cm^{-1}.

EXAMPLE 7

N-(2-n-Propylpentanoyl)alanine-N'-benzylamide.

The title compound was prepared from N-(2-propylpentanoyl) alanine methyl ester (3.67 g, 16 mmole) according to the procedure described in Ex. 6, except that a methanolic solution of benzylamine (1.5 molar excess) was used, and the reaction mixture was stirred under reflux for 24 hours. 1.4 g (4.6 mmole, 29%) of the title compound as a white solid, mp 139° C., was thus obtained.

Anal calc. for $C_{18}H_{28}N_2O_2$: C, 71.01; H, 9.27; N, 9.21; Found: C, 70.88; H, 9.15; N, 9.24.

^{1}H NMR δ (DMSO): 7.25 (m, 6H, $PhCH_2NH$), 6.40 (br d, 1H, CONH), 4 61 (quintet, 1H, ala CαH), 4.39 (m, 2H, Ph—CH_2), 2.06 (m, 1H, Pr_2CH) 1.50, 1.25 (m, 8H, $CH_3CH_2CH_2$), 1.34 (d, 3H, ala Me), 0.87 (t, 3H, Me), 0.82 (t, 3H, Me) ppm.

MS: 304 (M^+,34), 198 (M^+–$PhCH_2NH$, 11), 171 (44).

IR: 3280, 2945, 2925, 1640, 1550, 1445 cm^{-1}.

EXAMPLE 8

N-(2-Propylpentanoyl)glycine-N'-methylamide.

The title compound was prepared from N-(2-propylpentanoyl)glycine methyl ester (5.0 g, 23.2 mmole) and 35% aqueous methylamine (56.4 mmole), according to the procedure described in Ex. 7. 2.86 g (13.4 mmole, 58%) of a white crystalline solid, mp 146° C., was thus obtained.

Anal. calc. for $C_{11}H_{22}N_2O_2$: C, 61.65; H, 10.35; N, 13.07; Found: C, 61.36; H, 10.14; N, 12.78.

^{1}H NMR δ (DMSO): 7.99 (br t, 1H, $CONHCH_2$), 7.69 (m, 1H, $CONHCH_3$), 3.62 (d, 2H, gly CH_2), 2.58 (d, 3H, NH Me), 2.22 (m, 1H, Pr_2CH), 1.45, 1.22 (m, 8H, $CH_3CH_2CH_2$), 0.83 (t, 6H, Me) ppm.

MS: 215 (MH^+,100), 197 (MH^+–H_2O, 23), 184 (MH^+–$MeNH_2$, 65), 127 (8).

IR: 3300, 2960, 2920, 2870, 1660, 1630, 1555, 1440, 1420 cm^{-1}.

EXAMPLE 9

N-(2-n-Propylpentanoyl)glycine-N'-butylamide.

The title compound was prepared from N-(2-propylpentanoyl)glycine methyl ester (5.0 g, 23.0 mmole) and butylamine (4.1 g, 55.0 mole), according to the procedure described in Ex. 7. 2.2 g (8.5 mmole, 37%), mp 101° C., was thus obtained.

Anal. calc. for $C_{14}H_{28}N_2O_2$: C, 65.58; H, 11.01; N, 10.93; Found: C, 65.87; H, 11.23; N, 11.38.

^{1}H NMR δ (DMSO): 7.99 (br t, 1H, NH), 7.65 (br t, 1H, NH), 3.63 (d, 2H, gly CH_2), 3.05 (m, 2H, $CH_3CH_2CH_2CH_2NH$), 2.22 (m, 1H, Pr_2CH), 1.50–1.16 (m, 12H, $CH_3CH_2CH_2CH_2NH$), 0.85 (t, 3H, $CH_3CH_2CH_2NH$), 0.83 (t, 3H, $CH_3CH_2CH_2$) ppm.

MS: 257 (MH^+, 100), 184 (MH^+–$C_4H_9NH_2$, 19).

IR: 3300, 2940, 1660, 1635, 1555, 1470, 1435, 1300 cm^{-1}.

EXAMPLE 10

N-2-n-Propylpentanoyl)glycine-N'-methylamide.

The title compound was prepared from valproyl chloride (404 mg, 2.5 mmole) and 2-amino-N-methylacetamide (220 mg, 2.5 mmole, prepared from glycine methyl ester hydrochloride and methylamine), according to the procedure described in Ex. 1. 318 mg (1.49 mmole, 59%) of a white crystalline solid was thus obtained, identical to the product described in Ex. 8.

EXAMPLE 11

N-(2-n-Propylpentanoyl)-4-aminobutyramide.

To an ice-cooled solution of N-(2-propylpentanoyl)-4-aminobutyroyl chloride (prepared from N-(2-propylpentanoyl)-4-aminobutyric acid and $SOC_{12,\ 5.9}$ g, 24.0 mmole) in dioxane (25 ml), was added dropwise conc. NH_4OH (34 ml) over 1 hr. The reaction mixture was then stirred at RT for 20 hrs and evaporated to dryness under reduced pressure. The residue was taken up in an H_2O (20 ml) and EtOAC (30 ml) mixture, the mixture stirred vigorously for 5 min. The organic phase was separated, evaporated to dryness under reduced pressure, and the residue crystallized from EtOAc to give 1.4 g (6.1 mmole, 26%) of a crystalline solid, mp 138° C.

Anal calc for $C_{12}H_{24}N_2O_2$: C, 63.13; H, 10.60; N, 12.27; Found: C, 63.12; H, 10.69; N, 12.54.

^{1}H NMR δ (DMSO): 7.81 (br t, 1H, NH), 7.26 (br s, 1H, $(CH_2)3CONH_2$), 6.73 (br s, 1H, $(CH_2)_3CONH_2$), 3.02 (m, 2H, $CH_2CH_2CH_2CONH_2$), 2.11 (m, 1H, Pr_2CH), 2.03 (t, 2H, CH_2CONH_2), 1.58 (m, 2H, $CH_2CH_2CONH_2$), 1.42 (m, 2H, CH_2CHCO), 1.19 (m, 6H, CH_2CH_2CHCO), 0.84 (t, 6H, Me) ppm.

MS: 229 (MH_+, 100), 127 (17).

IR: 3405, 3300, 3190, 2960, 2935, 2880, 1660, 1655, 1635, 1550, 1445 cm^{-1}.

EXAMPLE 12

N-[2-n-Propylpent-(E)-2-enoyl]glycinamide.

A cold solution of glycinamide hydrochloride (6.63 g, 60 mmole) in water (18 ml) and Et_3N (12.7 g, 126 mmole) were added slowly to a stirred and ice-cooled solution of (E)-2-ene-valproyl chloride in toluene (40 ml). After completion of addition, the biphasic reaction mixture was stirred at ambient temperature for 3 hrs. Work-up and crystallization according to the procedure in Ex. 1 afforded 6.92 g (34.8 mmole, 58%) of the title compound as a white crystalline solid, mp 112° C.

Anal. calcd. for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.13; N, 14.13; Found: C, 60.53; H, 8.86; N, 14.04.

^{1}H NMR δ ($CDCl_3$): 6.97 (br s, 1H, $CONH_2$), 6.91 (br t, 1H, NH), 6.29 (t, 1H, vinyl), 6.05 (br s, 1H, $CONH_2$), 2.28 (m, 2H, CH_3CH_2CH=), 2.17 (m, 2H, $CH_3CH_2CH_2$), 1.42 (m, 2H, $CH_3CH_2CH_2$), 1.05 (t, 3H, Me), 0.93 (t, 3H, Me) ppm.

MS: 199 (MH^+, 83), 182 (MH^+–NH_3, 79), 125 (100).

IR: 3341, 3179, 2955, 2872, 1680, 1601, 1535, 1433, 1319 cm^{-1}.

EXAMPLE 13

N-[2-n-Propylpent-(E)-2-enoyl]alanine methyl ester.

The title compound was prepared from (E)-2-enevalproyl chloride (10.95 g, 68.1 mmole) and alanine methyl ester hydrochloride (10.14 g, 72.6 mmole) according to the procedure described in Ex. 4. The crude product was crystallized from hexane to give 13.25 g (58.4 mmole, 86%) of a white crystalline solid, mp 25° C.

^{1}H NMR δ ($CDCl_3$): 6.30 (br d, 1H, NH), 6.23 (t, 1H, vinyl) 4.65 (m, 1H, ala CH), 3.76 (s, 3H, OMe), 2.29 (m, 2H, $CH_3\underline{CH_2}CH$=), 2.17 (m, 2H), 1.43 (d, 3H, ala CH_3), 1.43 (m, 2H, $CH_3\underline{CH_2}CH_2$), 1.04 (t, 3H, Me), 0.92 (t, 3H, Me) ppm.

MS: 228 (MH^+, 100), 196 (NH^++–NH_3, 100), 168 (30), 125 (76).

EXAMPLE 14

N-[2-n-Propylpent-(E)-2-enoyl]glycine-N'-methylamide.

The title compound was prepared from N-[2-n-propylpent-(E)-2-enoyl]glycine methyl ester (13.5 g, 63.9 mmole), prepared from 2-ene-valproyl chloride and glycine methyl ester hydrochloride as described in Ex. 5, and 35% aqueous methylamine (15 ml, 169.2 mmole), according to the procedure described in Ex. 7. The amide product was purified by column chromatography and crystallized from EtOAc to give 7.8 g (36.8 mmole, 58%) of a white crystalline solid, mp 68°–9° C.

Anal. caled. for $C_{11}H_2ON_2O_2$: C, 62.23; H, 9.50; N, 13.20; Found: C, 62.42; H, 9.50; N, 13.05.

^{1}H NMR δ (DMSO): 7.94 (br t, 1H, NH) 7.67 (m, 1H, $\underline{NH}CH_3$), 6.23 (t, 1H, vinyl), 3.65 (d, 2H, gly), 2.58 (d, 3H, $NH\underline{CH_3}$), 2.21 (m, 2H, $CH_3\underline{CH_2}CH$=), 2.13 (m, 2H, $CH_3CH_2\underline{CH_2}$), 1.32 (m, 2H, $CH_3\underline{CH_2}CH_2$), 0.99 (t, 3H, Me), 0.85 (t, 3H, Me) ppm.

MS: 213 (MH^+, 73), 195 (37), 182 (MH^+–CH^+3NH_2, 100), 125 (74).

IR: 3300, 2955, 2925, 1660, 1620, 1560, 1540, 1460 cm^{-1}.

EXAMPLE 15

N-[2-n-propylpent-(E)-2-enoyl]alaninamide.

The title compound was prepared from N-[2-n-propylpent-(E)-2-enoyl]alanine methyl ester (9.08 g, 40 mmole) and aqueous ammonia (67 ml), in a manner analogous to that described in Ex. 6, giving 5.0 g (59%) of a white crystalline solid, mp 141°–2° C.

Anal. calcd. for $C_{11}H_{20}N_2O_2$: C, 62.23; H, 9.50; N, 13.20; Found: C, 62.48; H, 9.25; N, 13.18.

^{1}H NMR δ (DMSO): 7.63 (d, 1H, NH) 7.25 (br s, 1H, $CONH_2$), 6.96 (br s, 1H, $CONH_2$), 6.18 (t, 1H, vinyl) 4.25 (m, 1H, ala CH), 2.21 (m, 2H, $CH_3CH_2\underline{CH_2}$), 1.31 (m, 2H, $CH_3\underline{CH_2}CH$=), 2.11 (m, 2H, $CH_3CH_2\underline{CH_2}$), 1.31 (m, 2H, $CH_3\underline{CH_2}CH_2$), 1.23 (d, 3H, ala CH_3), 0.99 (s, 3H, Me), 0.84 (s, 3H, Me) ppm.

MS: 213 (MH^+, 74), 196 (MH^+–NH_3, 100), 125 (76).

IR: 3725, 3180, 2950, 1700, 1650, 1605, 1530, cm^{-1}

EXAMPLE 16

N-(2-n-Propylpentanoyl)-β-alaninamide.

A mixure of N-(2-n-propylpentanoyl)-β-alanine ethyl ester (4.45 g, 18.29 mmole), prepared from valproyl chloride and β-alanine ethyl ester hydrochloride according to the procedure described in Ex. 4, dry formamide (2.74 g, 61.27 mmole) and anhydrous THF (9.2 ml) was heated to 100° C., and a freshly prepared solution of sodium methoxide (12.7 mmole) in MeOH (2.93 ml) was added dropwise over 20 min. The mixture was heated at 100° C. for 4 hours and isopropanol (100 ml) was added. The suspension was heated to reflux, filtered, and the filtrate was evaporated to dryness. The residue was dissolved in a refluxing mixture of water and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (4×100 ml). The combined organic layers were washed with water, dried, and evaporated to dryness. The crude product (2.5 g) was crystallized from EtOAc to give 2.20 g (10.28 mmole, 56%) of a white solid, mp 167°–8° C.

Anal. calcd. for $C_{11}H_{22}N_2O_2$: C, 61.64; H, 10.35; N, 13.08. Found: C, 61.41; H, 10.16; N, 12.91.

^{1}H NMR δ (DMSO): 7.82 (br t, 1H, CONH), 7.29 (br s, 1H, $CONH_2$), 6.79 (br s, 1H, $CONH_2$), 3.20 (q, 2H, β-ala), 2.21 (t, 2H, α-ala), 2.12 (m, 1H, $(Pr)_2\underline{CH}$), 1.41, 1.18 (m, 8H, $CH_3CH_2CH_2$), 0.83 (t, 6H, Me) ppm.

MS: 215 (MH^+, 100), 197 (MH^+–$NH_{3,\ 69}$), 172 (13), 127 (3).

IR: 3389, 3303, 3202, 2957, 2928, 1653, 1634, 1551, 1456, 1439 cm^{-1}.

EXAMPLE 17

N-(2-n-Propylpentanoyl)threoninamide.

A solution of valproyl chloride (3.15 g, 19.4 mmole) in anhydrous 1,2-dimethoxyethane (DME, 48 ml) was added slowly to a suspension of threoninamide hydrochloride (3.0 g, 19.4 mmole) and Et_3N (3.88 g, 38.8 mmole) in anhydrous DME (60 ml) at 10°–15° C. The reaction mixture was stirred for 24 hours at RT under N_2; the solvent was removed under reduced pressure, and the residue was worked up in a manner analogous to that in Ex. 16. The product was crystallized from EtOAc to give 1.0 g (4.1 mmole, 21%) of a white solid, mp 172°–4° C.

Anal. calcd. for $C_{12}H_{24}N_2O_3$: C, 58.99, H, 9.90; N, 11.47; Found: C, 58.12; H, 9.42; N, 11.43.

^{1}H HMR δ (DMSO): 7.58 (d, 1H, CONH), 7.05 (br s, 2H, $CONH_2$), 4.84 (d, 1H, OH), 4.18 (dd, 1H, α-thr), 3.99 (m, 1H, β-thr), 2.35 (m, 1H, $Pr_2\underline{CH}$), 1.44, 1.22 (m, 8H, CH_3 $\underline{CH_2}\underline{CH_2}$), 1.02 (d, 3H, Me-thr), 0.85 (t, 3H, Me), 834 (t, 3H, Me) ppm.

MS: 245 (MH^+, 37), 228 (MH^+–NH_3, 100).

IR: 3405, 3281, 2957, 2930, 2854, 1688, 1665, 1624, 1549 cm^{-1}.

EXAMPLE 18

N-(2-n-Propylpentanoyl)glycine-N',N'-dimethylamide.

N-(2-n-Propylpentanoyl)glycine methyl ester (6.0 g, 29.9 mmole) prepared from valproyl chloride and glycine methyl ester hydrochloride according to the procedure in Ex. 4 was dissolved in MeOH (15 ml) and 40% aqueous dimethylamine (11 ml) was added dropwise. The reaction mixture was refluxed for 19 hr and evaporated to dryness. The reaction mixture was treated with hot ethyl acetate, cooled, and filtered. The filtrate was washed consecutively with sat. $NaHCO_3$ and sat. NaCl solution, dried and evaporated to dryness. The solid residue was crystallized from ethyl acetate/hexane to give 1.50 g of a white solid, mp 78°–80° C.

Anal. calcd. for $C_{12}H_{24}N_2O_2$: C, 63.12, H, 10.59; N, 12.27. Found: C, 62.80, H, 10.64; N, 11.93.

^{1}HNMR δ (DMSO): 7.73 (br t, 1H, CONH), 3.79 (d, 2H, gly), 2.84 (s, 3H, Me), 2.72 (s, 3H, Me), 2.16 (m, 1H, $(Pr)_2$ $\underline{CH}$), 1.34 (m, 2H), 1.12 (m, 6H), 0.74 (t, 6H, Me) ppm.

MS: 229 (MH^+, 100), 184 (18).

IR: 3314, 2951, 2924, 2872, 1662, 1630, 1522, 1466 cm^{-1}.

EXAMPLE 19

Biological Activity of N-(2-Propylpentanoyl)glycinamide.

All compounds provided herein were screened for their ability to protect against chemically and electrically induced convulsions, in at least two different models of epilepsy. The first model, the subcutaneous pentylenetetrazol (s.c. Met) seizure threshold test, is a standard screening procedure to show efficacy for agents against absence seizures. The second model, the maximal electroshock (MES) test, is used to show efficacy for antiepileptic agents against generalized seizures. In these studies, convulsions were inhibited or prevented in mice after intraperitoneal (i.p.) administration and/or in rats after oral (p.o.) administration of the compounds.

N-(2-Propylpentanoyl)glycinamide (hereinafter compound 1) was further tested in two additional models. The third model, electrical kindling of rats, has been known to show efficacy of antiepileptic agents against complex partial seizures that evolve into generalized motor seizures. In these tests, rats were electrically stimulated via corneal electrodes twice daily for approximately 5 days and then once daily for an additional 10 days. Once the seizure criteria, as described by R. J. Racine, et al., *Electroenceph. Clin. Neurophysiol.*, 32: 281–294 (1972), were met, the test substance was administered p.o. to rats, and the rat electrically stimulated, and observed for the presence or absence of a seizure. In addition, compound 1 was also tested in the subcutaneous bicuculline model (s.c. Bic). For detailed procedures of all the above test models, see E. A Swinyard, et al , in "Antiepileptic Drugs," ed. by R. H. Levy, et al., Raven Press, New York, at 85–100 (1989) and Racine, Id.

Compound 1 showed anticonvulsant activity in rodents in all of the above mentioned tests (MES, s.c. Met, s.c. Bic, and electrical kindling models). The ED50 (rat, p.o.) in the MES model was 73 mg/kg (Table 1). This value is seven times lower (more efficacious) than that found for VPA, and approximately twice that found for phenytoin (Table 1; see E.A. Swinyard, et al., id.). Further, in the electrically kindled rat model, compound 1 (administered p.o.) prevented seizures with an ED_{50} of 162 mg/kg (Table 1). The results are therefore indicative of compound 1 having an efficacy against generalized seizures and complex partial seizures which evolve into generalized motor seizures.

In addition, in the s.c. Bic model, compound 1 provided full protection from seizures in mice, at a dose that was approximately that of literature values for the ED_{50} for VPA. Literature values also show that phenytoin, considered the drug of choice for partial and generalized tonic-clonic seizures, is not effective in this model. See B. J. Wilder and R. J. Rangel, in "Antiepileptic Drugs," ed. by R. H. Levy, et al., Raven Press, New York, at 233–239 (1989).

In the s.c. Met model (mice, i.p.), the ED_{50} for compound 1 was 127 mg/kg (Table 1) as compared to the literature value of 146 mg/kg for VPA. These results further indicate efficacy for compound 1 against absence seizures as well.

EXAMPLE 20

Neurotoxicity of Compound 1.

Neurotoxicity of the claimed agents was also assessed in mice (i.p. adminstration) by the rotorod ataxia test and also in some cases in rats (p.o. administration) by the positional sense test and gait and stance test. See E. A. Swinyard, et al., in "Antiepileptic Drugs," ed. by R. H. Levy, et al., Raven Press, New York, at 85–100 (1989). None of the agents provided in the invention showed neurotoxicity in mice at the test dose of 100 mg/kg. Compound 1 had a median neurological toxic dose (TD_{50}) in rats of more than 1000 mg/kg. By comparison, the TD_{50} for VPA was 280 mg/kg. In mice, the difference between TD_{50} values between compound 1 and VPA was smaller, but still significantly higher for compound 1 (less neurotoxic) (Table 1). The protective index (PI, $PI=TD_{50}/ED_{50}$) for compound 1 in rats tested in the MES test is more than 23 times greater than that found for VPA (Table 1). These results are shown to indicate that there is a larger therapeutic dose range that can be administered before neurological side effects are usually observed.

The median lethal dose (LD_{50}) of compound 1 in mice (i.p. administration) is more than 4,000 mg/kg. This value is in contrast to VPA whose LD_{50} in the same test was 658 mg/kg. The results, therefore, indicate that compound 1 is considerably less toxic than VPA.

EXAMPLE 21

Neurological Activity of Compound 1.

A major neurological side effect observed in patients on treatment with antiepileptic agents is cognitive impairment. Present data further indicate that at the minimum dose required to provide full protection from seizures induced in rats in the MES test, compound 1 results in less cognitive impairment than VPA. Results from the models used are taken as indicators of major constituents of human cognition.

The studies test for the level of motivation, association and short and long-term memory. The specific studies were the effect of compound 1 on the performance of rats in the locomotor test and passive and active response tests. In the cognitive studies below, doses used for compound 1 and VPA were the minimum doses which give full protection against seizures in the MES test (Compound 1=200 mg/kg and VPA=500 mg/kg).

In the locomotor test, motor activity was recorded 8 to 9 days after the beginning of drug treatment. Locomotion scores were recorded in cages (25×26cm) having a grid of infra-red beams at 4 cm intervals. Two categories of movements were recorded: small movements (those originating in stationary activities such as grooming and scratching), and big movements (those resulting in ambulation and recorded as the simultaneous crossing of more than two beams). Since rats are nocturnal animals, recordings were usually made between 18:00 PM–6:00 AM.

The results in the locomotor test (Table 2) show no significant difference in motor activity between the control and compound 1.

To measure passive avoidance responses, tests were performed on days 10, 12, 14, 20, and 26 after initiation of drug treatment. The apparatus consisted of a lit chamber that can be separated from a dark chamber by a sliding door. In the experiment, a rat is placed in a lit chamber for 30 sec, the door is then opened and the rat moves into the dark chamber with latency that is recorded. Upon entry into the dark chamber, the door is shut and a 0.3 mA footshock is delivered for 3 sec. Retention of the experience is determined after 48 hours by repeating the test and recording the latency. The maximum latency was arbitrarily assigned the value of 300 sec. Longer latencies are taken as a measure of improved memory.

Results from this study show that on day 16 of the test, the group receiving compound 1 retained their acquired knowledge to avoid the electric shock as well as the control group

(FIG. 1). The VPA-treated rats, however, were apparently affected by treatment, and performed much worse. These results suggest that VPA adversely affected memory, whereas compound 1 did not have this adverse effect.

The conditioned avoidance response (active avoidance test) of rats was determined in a Hugo-Basile automatic conditioning apparatus, which consists of a shuttle box with two separate floor grids. In this apparatus the rats are conditioned to jump from one side of the box to the other side. The conditioning is a 10 sec stimulus consisting of a light and electric buzzer. At the end of this stimulus the rats which do not jump to the other side of the box receive a 20 sec electroshock (50 V, 0.3 mA) from the grid floor. The rats that do jump to the other side of the box do not receive the shock. The session is then repeated with the same rats 7 days later. Experiments were carried out on days 16–17 and 22–23 from the start of drug treatment, and each rat received 60 trials with a 30 sec interval between each trial.

The following parameters were recorded: a) the number of potential shocks successfully avoided; b) the latency response in seconds for avoiding a potential shock; and c) the total number of crossings made throughout the trials. In this test, a better performance is indicated by an increase in the avoidance of an electric shock, a decrease in the latency time to jump to the other side of the cage, and an increase in the number of times the rats crossed to the other side of the cage.

Rats treated with compound 1 showed a significantly better performance than the VPA treated group. The performance of the animals treated with compound 1 was similar to that of the control group, whereas the VPA-treated rats had a worse performance (FIG. 2 and Table 3).

The tests stated hereinabove are consistent with the conclusion that compound 1 causes less cognitive impairment than VPA.

Based on the lower ED_{50} and on the higher TD_{50} and LD_{50} values of compound 1, as compared to those of VPA, the former may be considered to act by a unique mechanism, and not as a prodrug of VPA. Moreover, these results are quite unexpected in view of the fact that neither valproylglycine nor milacemide was active when tested in mice (i.p. administration at doses up to 300 mg/kg), in the MES and s.c. Met models.

TABLE 1

Anticonvulsant profile of the claimed and reference antiepileptic agents.

COMPOUND	COMPOUND 1 (mg/kg)	Phenytoin (mg/kg)	Valproic acid (mg/kg)	Carbamzaepine (mg/kg)
Rat p.o TD50 MES model	>1000	>3000	281	813
ED50	73	29.8	490	8.5
Pi	>13.7	100	0.6	95.7
s.c. MET model				
ED50	—	N.E.	180	N.E.
Pi	—	—	1.6	—
Electrical kindling model ED50	162	—	117	28.9
Mice i.p. TD50	369	65.5	426	71.6
MES model				
ED50	152	9.5	272	
PI	2.4	6.9	1.6	8.1
s.c. MET model				
ED50	127	N.E.	149	N.E.
PI	2.9	—	2.9	

The anticonvulsant profile of compound I compared to literature values (for anticonvulsant activity whose experimental protocols were identical to those carried out in the current study) for the prototype anticonvulsant agents VPA and phenytoin. Convulsions were induced in mice and rats by subcutaneous administration of pentylenetetrazol (s.c. Met test) or by electrical stimulation (MES test). N.E. = not effective.

TABLE 2

Activity scores of rats chronically treated with compound 1.

	Day activity 14.00–20.00 h		Night activity 20.00–08.00 h	
Treatment	Big mov.	Total mov.	Big mov.	Total mov.
Control (7)	1939 ± 349	6391 ± 983	6124 ± 489	23750 ± 2075
compound 1 (7)	2402 ± 307	7749 ± 1188	7217 ± 765	22568 ± 2209

TABLE 2-continued

Activity scores of rats chronically treated with compound 1.

Treatment	Day activity 14.00–20.00 h		Night activity 20.00–08.00 h	
	Big mov.	Total mov.	Big mov.	Total mov.
Na Valproate 500 mg/kg (6)	2784 ± 352	8963 ± 1554	5832 ± 854	18876 ± 2039

Activity scores of drug-treated rats, measured in activity cages on days 8–9 after initiation of daily oral dosing with the given drug. Figures are number of crossings ± SEM. Number of rats per group are given in parenthesis.

TABLE 3

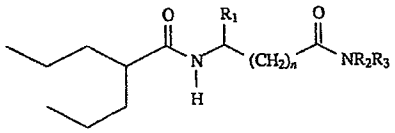
Active avoidance response of claimed and reference compounds.

	Drug treatment					
	Session I			Session II		
	Avoidance	Latency	Crossings	Avoidance	Latency	Crossings
Control (7)	9 ± 5	23 ± 3	32 ± 10	9 ± 5	25 ± 2	30 ± 10
compound 1 200 mg/kg (7)	14 ± 7	21 ± 3	38 ± 13	12 ± 7	22 ± 3	35 ± 9
Carbamizepine 15 mg/kg (4)	7 ± 4	27 ± 2	18 ± 10	2 ± 2	29 ± 1	11 ± 8
Na Valproate 500 mg/kg (6)	2 ± 3	28 ± 0.4	13 ± 2	6 ± 5	27 ± 2	16 ± 9

Scores in the active avoidance test (conditioned avoidance response) of rats treated with compound 1 and related drugs. The tests in the first session were performed on days 16–17 from initiation of drug administration. Those in session II were performed on days 22–23, that is 7 days following session I. Number of rats in a group are given in parenthesis.

What is claimed is:

1. A compound having the structure:



wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1–C_6 alkyl group, an aralkyl group, or an aryl group, and n is equal to 0.

2. The compound of claim 1, wherein the C_1–C_6 alkyl group is a linear chain alkyl group.

3. The compound of claim 1, wherein the C_1–C_6 alkyl group is a branched chain alkyl group.

4. The compound of claim 1, wherein the aralkyl group is a benzyl, alkylbenzyl, hydroxybenzyl, alkoxycarbonylbenzyl, aryloxycarbonylbenzyl, carboxybenzyl, nitrobenzyl, cyanobenzyl, or halobenzyl group.

5. The compound of claim 1, wherein the aryl group is a phenyl, naphthyl, anthracenyl, pyridinyl, indolyl, furanyl, alkylphenyl, hydroxyphenyl, alkoxycarbonylphenyl, aryloxycarbonylphenyl, nitrophenyl, cyanophenyl, halophenyl group, mercaptophenyl, or aminophenyl group.

6. A compound of claim 1 selected from the group consisting of:

N-(2-n-propylpentanoyl)glycinamide;

N-(2-n-propylpentanoyl)glycine-N'-methylamide;

N-(2-n-propylpentanoyl)glycine-N'-butylamide;

N-(2-n-propylpentanoyl)leucinamide;

N-(2-n-propylpentanoyl)alanine-N'-benzylamide;

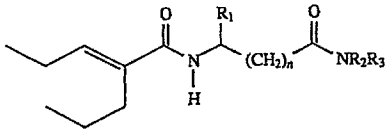
N-(2-n-propylpentanoyl)alapinamide;

N-(2-n-propylpentanoyl)-2-phenylglycinamide;

N-(2-n-propylpentanoyl)threoninamide; and

N-(2-n-propylpentanoyl)glycine-N',N'-dimethylamide.

7. A compound having the structure:



wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1–C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3.

8. The compound of claim 7, wherein the C_1–C_6 alkyl group is a linear chain alkyl group.

9. The compound of claim 7, wherein the C_1–C_6 alkyl group is a branched chain alkyl group.

10. The compound of claim 7, wherein the aralkyl group is a benzyl, alkylbenzyl, hydroxybenzyl, alkoxycarbonylbenzyl, aryloxycarbonylbenzyl, carboxybenzyl, nitrobenzyl, cyanobenzyl, or halobenzyl group.

11. The compound of claim 7, wherein the aryl group is a phenyl, naphthyl, anthracenyl, pyridinyl, indolyl, furanyl, alkylphenyl, hydroxyphenyl, alkoxycarbonylphenyl, aryloxycarbonylphenyl, nitrophenyl, cyanophenyl, halophenyl group, mercaptophenyl, or aminophenyl group.

12. A compound of claim 7 selected from the group consisting of:

N-(2-n-propylpent-2-enoyl)glycinamide;

N-(2-n-propylpent-2-enoyl)alaninamide; and

N-(2-n-propylpent-2-enoyl)glycine-N'-methylamide.

13. A pharmaceutical composition which comprises the compound of claims 1 or 7 or a in a therapeutically effective amount and a pharmaceutically acceptable carrier.

14. The pharmaceutical composition of claim **13** wherein the therapeutically effective amount is an amount from about 10 to about 500 mg.

15. The pharmaceutical composition of claim **14**, wherein the carrier is a solid and the composition is a tablet.

16. The pharmaceutical composition of claim **14**, wherein the carrier is a gel and the composition is a suppository.

17. The pharmaceutical composition of claim **14**, wherein the carrier is a liquid and the composition is a solution.

18. A method of treating a subject afflicted with epilepsy which comprises administering to the subject an amount of the compound of claim **7** effective to treat epilepsy in the subject.

19. A method of treating a subject afflicted with epilepsy which comprises administering to the subject an amount of the compound of claim **1** effective to treat epilepsy in the subject.

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